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RABIES.

A REVIEW OF RECENT ARTICLES. XVII.*

i. *Virus.*

Further information regarding the epidemic in Trinidad which was described in detail in the previous review of this series (this *Bulletin*, Vol. 29, p. 187) is now available.

HURST and PAWAN[1] describe the histological and experimental findings relating to 5 cases in man, and 5 cases in cattle. A diagnosis of rabies was experimentally established in 3 of the human cases, and in all the cattle cases. The virus was transmitted to monkeys and in the brains of these Negri bodies were invariably found. Cross-immunity tests were carried out with fixed virus (Paris strain) and with two strains of Trinidad virus, one from a human case, the other from a cow. Immunization was carried out by Semple's method. The results show that immunization with fixed virus protected in a certain number of cases against the intracerebral inoculation of the Trinidad virus, whilst immunization with the Trinidad virus protected to a much lesser degree against fixed virus. The results of serum neutralization tests with the various sera against fixed virus, Trinidad virus, and a Paraguayan rabic virus supplied by REMLINGER, showed evidence of a similar cross immunity. In three of the human cases now reported there was a definite history of bite by a bat. This is however stated to be a not uncommon occurrence in Trinidad. "On the whole though final proof is lacking, the evidence available suggests the vampire bat as the vector of the disease." The lesions in the recent Trinidad human cases agree well with those recorded in the majority of cases of paralytic rabies. The spinal cord shows wide-spread nerve destruction with considerable microglial proliferation, and variable perivascular infiltration with exudation of polymorphs. The anterior and posterior horns are equally affected, thus differing from the appearances in poliomyelitis.

* For the sixteenth of this series see Vol. 29, pp. 187–195.

[1] HURST (E. Weston) & PAWAN (J. L.). A Further Account of the Trinidad Outbreak of Acute Rabic Myelitis: Histology of the Experimental Disease.—*Jl. Path. & Bact.* 1932. May. Vol. 35. No. 3. pp. 301–321. With 7 plates. [11 refs.]

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A full report on the Trinidad virus is published by REMLINGER and BAILLY.[2] They have been able to transmit the infection with the greatest regularity to rabbits, guineapigs, dogs, cats, etc. It is a true rabies virus. The various characteristics of the Trinidad epidemic and epizootic are then discussed, as well as the mode of transmission.

TORRES[3] has carried out a series of experiments by which the results which he previously reported (this *Bulletin*, Vol. 29, p. 188) regarding the identity of the viruses of Santa Catherina and Matto Grosso with the virus of rabies, are confirmed. From experiments on 14 laboratory animals, he has been able to show that vaccination with the virus of Santa Catherina prevented infection with street and fixed viruses, and that vaccination with street and fixed virus conferred immunity against infection with the virus of Santa Catherina. Also vaccination with the virus of Matto Grosso conferred immunity in the case of two guineapigs against fixed virus. Control animals inoculated at the same time with fixed virus developed rabies in 4 to 5 days, with street virus in 11 to 17 days, and with the virus of Santa Catherina in 9 to 11 days. The vaccines employed consisted of 15 per cent. emulsions of brain substance, glycerinated to 30 per cent., and containing 0·5 per cent. phenol. These were heated for 24 hours at 42°C. Nine doses of 3 cc. were given to each animal. The test doses were 0·2 cc. of a 1 in 10 emulsion of brain substance inoculated intra-cerebrally.

KRAUS and DURAN[4] discuss epizootics of rabies amongst cattle and horses in South America. From the presence of Negri bodies in the brain, the infectivity of the brain substance when inoculated into rabbits and dogs, and the presence of Negri bodies in the brains of animals so inoculated, there can be no doubt that the virus of rabies is the causative agent. This virus differs in certain respects from the classic street virus. It is probably a variety of rabies virus. The epizootic is not spread by dogs. HAUPT and REHAAG consider that the carrier is the bat, and claim that the brains of bats contain Negri bodies and are infective when inoculated into rabbits.

A virus from a case of pseudo rabies has been examined by PATTO.[5] It emanated from a cow which died in Varginha (Brazil) in 2 or 3 days after exhibiting symptoms of pruritus, hyperaesthesia and extreme agitation. When introduced into animals the virus induced in 2–5 days pruritus, hyperaesthesia, agitation, and aggressiveness, and death followed rapidly. Paralysis was rarely observed, and only as an agonal symptom. No Negri or Manouélian bodies, or other cell inclusions, were found post-mortem. Experimental transmission of the disease was most easily brought about by the subdural route. Vaccination with the virus conferred a definite immunity against

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[2] REMLINGER (P.) & BAILLY (J.). Contribution à l'étude du virus de la Trinité.—*Bull. Acad. Méd.* 1932. Feb. 16. 96th Year. 3rd Ser. Vol. 107. No. 7. pp. 242–253. [11 refs.]

[3] TORRES (Sylvio). A raiva no Brasil. Verificações sobre a immunidade crusada.—*Rev. Zootecnia e Vet.* 1931. Vol. 17. No. 3. pp. 266–270. French summary.

[4] KRAUS (R.) & DURAN (Agustin). Ueber die in Südamerika vorkommenden Epidemien der Hundswut bei Rindern und Pferden (Mauleseln).—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1932. Vol. 74. No. 1/2. pp. 182–199.

[5] PATTO (Ortiz). Estudo de um virus neurotropo de pseudolyssa.—*Brasil-Medico.* 1931. Dec. 19. Vol. 45. No. 51. pp. 1190–1195.

the disease, but not against the virus of rabies (2 guineapigs), and vaccination with rabies virus did not protect against the virus in question (2 guineapigs).

NICOLAU, MATHIS, and CONSTANTINESCO[6] have made a detailed study of a strain of virus of Oulou-Fato recovered from the brain of a child which died at Dakar 36 days after having been bitten on the forearm, and at the 16th day of Pasteurian treatment, without exhibiting the usual acute symptoms of rabies. Inclusion bodies resembling Negri bodies were found in the brain; inoculation into the brains of two rabbits produced paralysis and death, Negri bodies being observed in the brain substance, whilst inoculation of the virus after three passages through rabbits, did not affect a rabbit which had been previously immunized against rabies. The virus was fixed with difficulty after a series of 20 subpassages through rabbit's brain. The incubation periods were as follows: 21, 20, 23, 18, 14, 12, 12, 11, 10, 9, 10, 8, 8, 9, 9, 8, 7, 8, 9 and 8 days. The characteristics of the strain in its original form are stated to be (1) feebleness of pathogenic action, (2) slow centrifugal dissemination along nerve paths, seldom reaching the salivary glands, (3) dilution greater than 1 in 500 did not convey infection subdurally. Though the saliva of the biting animal in the case of oulou-fato may often be avirulent, a course of antirabic treatment should, in the opinion of the authors, always be given to persons bitten by animals suffering from this form of rabies.

REMLINGER[7] wisely, in our opinion, criticizes the conclusions which NICOLAU and his co-workers have drawn. He does not admit from the shortness of the incubation in the child that the strain was attenuated. He does not admit that failure to find evidence of infectivity in the saliva is a proof of slow centrifugal dissemination, as such infectivity is known to be irregular. Difficulties in fixing strains of ordinary street virus are frequently met with. Some fix rapidly, some slowly. NICOLAU replies to this criticism, at the end of REMLINGER'S paper.

A strain of street virus from Brazzaville (French Equatorial Africa) has been examined by VAUCEL, BOISSEAU, and SALAÜN[8] by crossed immunization experiments, which show that, as in the case of the strain from French West Africa examined by REMLINGER, it is identical with the rabies virus of Europe. "The only difference between the viruses of Africa and the virus of Europe is the lower virulence of the former for man."

REMLINGER and BAILLY[9] discuss the endemicity of rabies in Morocco. In general it is believed that the rabies of Africa and of Western Europe is less virulent in type than that of Russia, the Balkan States, and of Asia. But in the last few years a number of fatal cases have occurred in Morocco in spite of treatment. The authors considered

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[6] NICOLAU (S.), MATHIS (C.) & CONSTANTINESCO (Val.). Sur un virus de l'Oulou-Fato (maladie du chien fou) isolé chez l'homme.—*Bull. Soc. Path. Exot.* 1931. Dec. 9. Vol. 24. No. 10. pp. 931–939. [Refs. in footnotes.]

[7] REMLINGER (P.). L'Oulou-Fato n'est-il qu'une rage atténuée?—*Bull. Soc. Path. Exot.* 1932. Feb. 10. Vol. 25. No. 2. pp. 118–122.

[8] VAUCEL (M.), BOISSEAU (R.) & SALAÜN (G.). Rage canine en Afrique Equatoriale Française. (Identité du virus rabique de Brazzaville et du virus fixe de l'Institut Pasteur de Paris.)—*Bull. Soc. Path. Exot.* 1932. Mar. 9. Vol. 25. No. 3. pp. 191–196.

[9] REMLINGER (P.) & BAILLY (J.). La rage et le virus rabique au Maroc.—*Bull. Soc. Path. Exot.* 1932. Apr. 13. Vol. 25. No. 4. pp. 289–294.

it advisable to examine the virulence of various Moroccan strains with the object of determining whether the virulence of these strains was higher than normal. Virulence was tested by observing the incubation period in rabbits which had been inoculated subdurally with street virus. The results are as follows :—

(1) Virus of Tangiers : 48 brains tested : average incubation 14 days.

(2) Virus of Interior of Morocco : 14 brains tested : average incubation 17 days.

(3) Virus of Gibraltar : 6 brains tested : average incubation 16 days.

The average incubation periods when the virus was introduced into the muscles of the neck of guineapigs were respectively 18·7, 19, and 18 days. It appears then that the rabies of Morocco does not differ from that of western Europe.

BRANCHINI[10] has succeeded in subpassaging fixed virus of the rabbit through a series of 17 dogs, the inoculation being performed by the intraocular route. There was no shortening of the incubation period, which varied irregularly throughout the series. The periods from inoculation to death were as follows : 17, 10, 11, 19, 14, 10, 12, 8, 12, 17, 12, 14, 8, 9, 10, 16, 7, 14, 10, 11, —, 16 and 7 days. The period of incubation did not appear to vary with the breed, or the condition of the dogs.

It may be remembered (this *Bulletin*, Vol. 22, p. 243) that NICOLLE and BURNET attempted to reverse the alteration of street virus into fixed virus, which is brought about by passage in rabbits, by passaging fixed virus through dogs. At that time they had reached the 11th passage and had observed no modification. It is reported by NICOLLE and BALOZET[11] that the experiment has been continued throughout the interval of eight years and that the virus has now reached its 106th passage through dogs. No restoration of street virus characteristics has occurred. The period of incubation varies from 4 to 7 days ; and no Negri bodies have appeared in the brain of the dog. This result was adumbrated in my previous review (Vol. 22, p. 243).

A strain of virus of exalted virulence is described by BABLET and MARNEFFE.[12] A European bitten superficially at the base of the thumb died in spite of treatment after a period of 20 days. The symptoms were not definite enough to permit of an exact diagnosis, but inoculation into rabbits removed all doubts. The rabbits developed rabies in 8 days with typical paralysis.

The influence of five methods of dilution on the rabies virus has been investigated by SCHNEIDER and SALEM.[13] In the first one part of brain was emulsified in two parts of a solution containing equal parts of glycerine and physiological saline. In the second one part

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[10] BRANCHINI (B.) Sul virus fisso di cane.—*Pathologica.* 1931. Dec. 15. Vol. 23. No. 482. pp. 730–734. English summary (6 lines).

[11] NICOLLE (Charles) & BALOZET (L.). Essai de restauration du virus rabique fixe par passages intracérébraux sur le chien.—*C. R. Acad. Sci.* 1932. May 17. Vol. 194. No. 20. pp. 1706–1708.

[12] BABLET (J.) & MARNEFFE (H.). Un cas de rage produit par un virus rabique des rues à virulence renforcée observé à Hanoi.—*Ann. Inst. Pasteur.* 1932. Mar. Vol. 48. No. 3. pp. 301–307.

[13] SCHNEIDER (J. E.) & SALEM (L.). Rabies Virus as affected by Certain Diluents.—*Jl. Amer. Vet. Med. Assoc.* 1931. Nov. Vol. 79. No. 5. pp. 642–644.

of brain was emulsified in two parts of distilled water. In the third one part of brain was emulsified in two parts of salt solution. The emulsions were strained through 60 mesh bolting cloth. The third portion was further subdivided in 3 parts called parts 3, 4 and 5. To part 4 was added 1 per cent. chloroform, and to part 5, 1 per cent. of 90 per cent. phenol. After cold storage for 100 days with daily shaking, the various parts were tested for virulence. Before testing, each was diluted with an equal quantity of physiological saline. Two rabbits were inoculated with each of the 5 emulsions, the dose in each case being 0·1 cc. The 2nd and 3rd samples (diluents distilled water and salt solution respectively) invariably induced rabies in 6 and 7 days. The 1st, 4th and 5th samples failed to induce rabies within 20 days.

ii. *Symptoms.*

In the course of experiments on the virulence of spleen, liver and kidney of rabid animals REMLINGER and BAILLY[14] have observed symptoms of an unusual nature in certain guineapigs, particularly when the virus employed was an exalted strain from a cat. Certain of the guineapigs inoculated developed rabies of the usual type in 8 to 70 days. Others in the 3rd, 4th or 5th week showed emaciation, listlessness, loss of appetite, and sometimes fleeting paresis, and died in the course of 24 hours or even less. Subpassage into rabbits was not effective. Of 129 guineapigs thus inoculated, 19 died of rabies, 38 with the above symptoms, and 72 survived. On the other hand of 30 rabbits inoculated with similar material, 8 developed rabies, 2 died with the above symptoms (subpassages negative) and 20 survived. Apparently the guineapig is the more susceptible animal. The authors refer to the cachexia which follows the inoculation of filtrates of brain substance and leads to a similar fatal termination. "Invariably in these animals the passages are negative." REMLINGER in 1904 considered that these accidents were due to the toxin of rabies. "We are to-day a little less affirmative."

Two unusual cases of rabies are described by STUART and KRIKORIAN.[15] The first is one in which the incubation period was prolonged (12 months). The second is that of a man bitten by a calf which had symptoms suggestive of rabies (difficulty of swallowing, and progressive weakness of limbs). Rabies in the calf was diagnosed by laboratory methods. The man was not treated, and developed rabies 4 months after the bite. "With regard to this patient, it seems right to emphasize that at no time previously had he been exposed to any risk of infection with rabies virus." This is an extremely unusual case. (See this *Bulletin*, Vol. 21, p. 714 for a similar case reported by OUCHAKOFF).

[The fact that certain species of animals though freely susceptible to rabies, appear only very rarely, if ever, to transmit the disease in nature, is one of great interest. The rat, for example, is highly susceptible to infection by laboratory methods; that it does not transmit infection in nature is a fact for which we may be profoundly thankful. The Trinidad experience suggests that the vampire bat may not be

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[14] REMLINGER (P.) & BAILLY (J.). Sur les accidents mortels observés chez des cobayes inoculés avec des organes d'animaux morts de rage.—*C. R. Soc. Biol.* 1931. Dec. 4. Vol. 108. No. 35. pp. 859–861.

[15] STUART (G.) & KRIKORIAN (K. S.). Unusual Development of Rabies Symptoms in Man.—*Ann. Trop. Med. & Parasit.* 1932. Mar. 19. Vol. 26. No. 1. pp. 55–64. [24 refs.]

so harmless. The reason why in nature certain species do or do not transmit infection may lie in the habits of the animals concerned, but the view of MANOUÉLIAN and VIALA (this *Bulletin,* Vol. 25, p. 707) that the infectivity of saliva depends upon the presence in it of ganglia cells containing virus suggests that a comparative study of the histology of the glands and the salivary apparatus in the various animals might prove of interest].

iii. *Pathology.*

A finding of great interest is reported by NICOLAU and KOPCIOWSKA.[16] The accepted view that Negri bodies are not present in the hippocampus in fixed virus rabies in the rabbit, rests upon evidence deduced from sections stained for the most part by the method of Mann. The authors find that using the slow method of Giemsa (as advocated by LEVADITI, NICOLAU, and SCHOEN this *Bulletin,* Vol. 24, p. 760) Negri bodies may be found with constancy but in small numbers in the horn of Ammon. They measure 4 to 6 or 7μ., and have the characteristic internal structure. They have been found in rabbits infected both with the Paris strain of fixed virus, and with the D.K. and Mathis strains. Whilst they are of rare occurrence in the horn of Ammon, they are much more numerous in the "noyau optique basal."

"This formation lies under the optic chiasma, or under the optic tract, and consists of a large number of ganglion cells. These cells appear to react more actively, during the course of fixed virus rabies, by the formation of Negri bodies than do the other nerve cells of the encephalon." The authors have examined the brains of over 60 rabbits dead of fixed virus rabies. In each case 100 neurones of the basal optic nucleus, and 100 neurones of the hippocampus were scrutinized. The following numbers of Negri bodies were found :—With the Paris strain of fixed virus : 36 in the former and 1 in the latter ; 58 and 3 ; 23 and 0·5 (200 neurones were counted in this case) 27 and 2 etc. With the D.K. strain the numbers were 23 and 5, 57 and 4, 63 and 2, etc. With the Mathis strain 122 and 3, 87 and 6, 172 and 9, 69 and 5, etc. The relative proportions in street virus rabies are similar. As many as 4 or even 5 Negri bodies may be found in the same nerve cell in fixed virus rabies of the rabbit in this seat of election.—[It would appear that the seat of election described by THOMAS and JACKSON (this *Bulletin,* Vol. 28, p. 744) lies somewhat posterior to the group of ganglion cells described above. The importance of searching for Negri bodies in this region is thus further emphasized.]

The pathological anatomy of the brain of a man who died of rabies 6 to 7 days after the first appearance of symptoms is described by ROJAS.[17] He considers that the changes are extraordinarily similar in type and extent to those observed in the acute phase of epidemic encephalitis. The histological appearances are described in detail, and the communication is fully illustrated.

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[16] NICOLAU (M. S.) & KOPCIOWSKA (L.). Zone élective pour les corps de Negri chez les lapins morts de rage expérimentale â virus fixe.—*C. R. Acad. Sci.* 1932. May 23. Vol. 194. No. 21. pp. 1865–1867. With 4 text figs.

[17] ROJAS (Luis). Ein Beitrag zur pathologischen Anatomie der Lyssa beim Menschen.—*Arch. f. Psychiatrie.* 1932. Jan. 22. Vol. 96. No. 1. pp. 1–23. With 14 figs. [30 refs.]

The histological appearances in the brains of rabbits which have received a course of antirabic treatment by the method employed at the Pasteur Institute of Paris are described by NICOLAU, CRUVEILHIER and KOPCIOWSKA.[18, 19] These are mainly an interstitial infiltration of the basal region by mononuclear cells from the meninges. The cells are often grouped round the neurones like satellites. These histological modifications are most intense in rabbits killed from 1 to 17 days after the 15th injection of fixed virus. Thereafter they appear to diminish. They are not observed in the case of control animals treated with emulsions of normal brain.

In a second paper this research is further elaborated. The authors consider that the reactions observed are due to " a very light infectious process engendered by the virus-vaccine." The reactions consist in (a) a mobilization of the elements of defence—lymphocytes, plasma cells, macrophages, microglia cells, and proliferation of the capsular cells of the spinal ganglia ; (b) a peculiar disposition of Nissl bodies in the neurones of the spinal ganglia and the medulla ; and (c) a swelling of the nucleus in certain nerve cells.

SCHWEINBURG[20] has examined the infectivity of the liver, spleen, pancreas, adrenals, sciatic nerve and blood of 20 laboratory animals which died of fixed virus rabies, and 30 which died after inoculation with street virus. The percentages of infections were as follows :—

	Street virus.	Fixed virus.	Both viruses.
Sciatic Nerve	33	20	28
Adrenals	30	5	20
Spleen	23	5	16
Pancreas	17	0	10
Liver	7	0	4
Blood	3	0	2

In 3 out of 12 animals inoculated with street virus, and in 2 out of 8 inoculated with street virus, the testicles were found to be infective. In many of the positive cases the clinical picture in the first passage was uncertain, and further subpassage was necessary before a definite diagnosis could be made. The infectivity of the various organs was independent of the clinical type of the disease in the parent animal, and its type in the test animal was also independent of the organ inoculated. The experiments shed no light on the conditions which determine the type of the disease.

An interesting study of the antigenic properties of rabies virus has been made by HAVENS and MAYFIELD.[21] Immune sera were examined

[18] NICOLAU (S.), CRUVEILHIER (L.) & KOPCIOWSKA (L.). Modifications histologiques provoquées par la vaccination antirabique dans le système nerveux des lapins.—*C. R. Soc. Biol.* 1931. Dec. 4. Vol. 108. No. 35. pp. 871–875. With 2 text figs.

[19] NICOLAU (S.), CRUVEILHIER (L.) & KOPCIOWSKA (L.). Interprétations des modifications histologiques provoquées par la vaccination antirabique dans le système nerveux des lapins.—*C. R. Soc. Biol.* 1931. Dec. 11. Vol. 108. No. 36. pp. 937–940. With 2 text figs.

[20] SCHWEINBURG (Fritz). Ueber den Nachweis von Lyssavirus in verschiedenen Organen.—*Zent. f. Bakt.* I. Abt. Orig. 1932. Feb. 3. Vol. 123. No. 7/8. pp. 434–448. [12 refs.]

[21] HAVENS (Leon C.) & MAYFIELD (Catherine R.). The Antigenic Properties of Rabies Virus.—*Jl. Infect. Dis.* 1932. Apr. Vol. 50. No. 4. pp. 367–376.

by flocculation and complement fixation tests. The sera of 6 rabbits immunized with fixed virus caused flocculation of a 1 per cent. suspension of fixed virus brain substance in appropriate dilutions, but had no effect on similar suspensions of vaccinia virus brain, or of normal brain. And conversely, the sera of rabbits immunized against vaccinia caused flocculation of vaccinia virus brain but not of normal brain, nor except in very high concentration of rabies virus brain. It was observed that flocculation of rabies virus brain was more slowly brought about (6 to 24 hours) than that of vaccinia virus brain (2 to 6 hours). Immunization by injections of killed rabies virus was apparently as effective as immunization with living. The flocculation test was then applied to the brains of 16 rabid animals in whose brains Negri bodies were present. The immune serum caused flocculation in 15 of these, whilst it had no effect on the brain material of 19 dogs, one cat, and two cows which showed no evidence of rabies on microscopical examination.

Attention was then turned to complement fixation tests, using the "cocto-antigen" of KRAUS and MICHALKA (this *Bulletin*, Vol. 24, p. 224). The anticomplementary effect of rabbit serum is well known. The six rabies immune sera prepared in rabbits were all anticomplementary within the specific range of the sera as shown by the flocculation tests. To avoid this difficulty immune sera were prepared in the guineapig. Preliminary flocculation tests showed that the guineapig was more difficult to immunize against fixed virus than the rabbit; the titres were much lower. Complement fixation tests however showed (1) that normal brain tissue did not react with immune guineapig serum; (2) that the rabies immune sera fixed complement with rabies antigens but not with vaccinia antigen; and (3) that vaccinia immune sera fixed complement with vaccinia antigen but not with rabies antigens.

iv. *Methods of Treatment and Statistics.*

SATO and KODAMA[22] have carried out some interesting experiments on the purification of rabies virus by kaolin adsorption. An emulsion of fixed virus brain substance in dilution 1 in 10 was prepared. After having been frozen and thawed repeatedly to ensure that the cells were broken up, the emulsion was centrifuged for ½ an hour at 3,500 revolutions per minute, and the supernatant fluid was withdrawn and again diluted ten times. It appeared from initial experiments that adsorption of the virus from this fluid by kaolin took place most readily when the reaction was neutral or slightly acid, and that elution was most complete at a pH between 9·5 and 10·5. By successive adsorption and elution a purified vaccine was prepared from which the larger portion of tissue proteins had been removed. Little loss of virulence resulted from a single purification, but after three such treatments some slight loss occurred. The purified virus passed readily through Mandler's V, N and W, and Chamberland L1 and L2 filters at a pH of about 9·0.

In 1928 ABADJIEFF showed that fixed virus was killed by the action of a 5 per cent. solution of yatren in 3 hours at 37°C. (This *Bulletin*, Vol. 25, p. 708). He has now[23] used this killed vaccine in the treatment

[22] SATO (Shinichi) & KODAMA (Takeshi). Purification of Fixed Rabies Virus and Vaccinia Virus by Adsorption on Kaolin.—*Kitasato Arch. Experim. Med.* 1931. July. Vol. 8. No. 3. pp. 287–302.

[23] ABADJIEFF (Boris). Tollwut-Yatrenvaccine.—*Ztschr. f. Hyg. u. Infektionskr.* 1932. Jan. 16. Vol. 113. No. 2 & 3. pp. 582–585. With 1 text fig.

of 2,980 bitten persons. Of these 4 died—that is to say the mortality was 0·13 per cent.—and one case of transitory post vaccinal paralysis was observed. The method of preparation of the vaccine is as follows :—A 10 per cent. emulsion of brain substance in 4 per cent. yatren solution is prepared. This is placed in the incubator for 24 hours at 37°C. After testing for sterility the resulting suspension is diluted to 1 in 4 with 2 per cent. yatren solution, and filtered through gauze. Fifteen daily doses varying from 0·25 to 2·5 cc. are administered in cases of average severity, and in severe cases three further injections of 3, 3, and 4 cc. are given. The amount of brain substance for treatment of ordinary cases is 700 mgm.

VIALA[24] reports that of 531 persons treated at the Pasteur Institute at Paris none developed rabies, and no accidents of any sort occurred.

The activities of the Pasteur Institute at Riga are described by ADELHEIM.[25] From 1914 to 1930, 6,021 persons have been treated with cords dried for 24 hours, and preserved in glycerine. Eight of these contracted rabies (i.e. a mortality of 0·13 per cent.). No complications have been reported.

The method of Högyes-Phillips has been employed in Bulgaria by ABADJIEFF[26] from April 1929 to December 1930. Of 2,484 persons treated two died of rabies, that is to say the mortality was 0·08 per cent. No post-vaccinal paralysis were observed.

OUCHAKOV[27] gives statistics of treatment during the year 1929 at the Institute of Experimental Medicine (Leningrad), of 1,283 persons, of whom 4 (0·3 per cent.) died of rabies. The vaccine employed was that of Fermi, and it was also sent out to 15 subordinate treatment centres. At these 1,709 persons were treated with one fatality (mortality 0·06 per cent.).

The first review of antirabic statistics compiled at the instance of the Paris Conference of 1927, by the League of Nations (MCKENDRICK) is reviewed by HESSE.[28] (See also this *Bulletin*, Vol. 28, p. 247). In a second paper HESSE[29] gives statistics relating to the German Pasteur institutes for the year 1931. 174 individuals have received treatment, and in all cases the treatment has been successful. No paralytic accidents have been observed.

v. *Post Vaccinal Accidents.*

The clinical features of 20 cases of post-vaccinal paralyses which have occurred at Cairo since 1910 are described by MOFTAH and

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[24] VIALA (Jules). Les vaccinations antirabiques à l'Institut Pasteur en 1931.—*Ann. Inst. Pasteur.* 1932. May. Vol. 48. No. 5. pp. 676–679.

[25] ADELHEIM (R.). Ueber die Tätigkeit des Pasteur-Institutes (Wutschutzstation) zu Riga.—*Ztschr. f. Hyg. u. Infektionskr.* 1932. Mar. 19. Vol. 113. No. 4. pp. 690–699.

[26] ABADJIEFF (Boris). Die Tollwutbehandlung in Bulgarien nach der Methode von Högyes-Phillips.—*Ztschr. f. Hyg. u. Infektionskr.* 1932. Jan. 16. Vol. 113. No. 2 & 3. pp. 406–410.

[27] OUCHAKOV (V.). Service antirabique de l'Institut de Médecine expérimentale. (Rapport annuel pour l'année 1930.)—*Arch. Sci. Biol.* 1931. Vol. 31. No. 4. pp. 417–428. [In Russian. French summary.]

[28] HESSE (Erich). Neue Tatsachen zur Wutschutzbehandlung.—*Arch. f. Soziale Hyg. u. Demographie.* 1931. Vol. 6. No. 2. pp. 127–133.

[29] HESSE (Erich). Die Tätigkeit der deutschen Wutschutzstationen im Jahre 1931.—*Reichs-Gesundheitsblatt.* 1932. May 4. Vol. 7. No. 18. pp. 300–303.

NABIH.[30] During the period in question 27,060 persons were treated. (In a further case the biting animal—a camel—did not develop rabies when under observation. The patient received no vaccinal treatment, but was given a dose of 10 cc. of a serum which is once referred to as antirabic, and twice as antitetanic). The sequence of these cases is interesting. During the period 1910 to 1926, 13 cases occurred, varying in degree from a slight facial paralysis to a severe Landry's ascending paralysis. All recovered after a convalescence more or less prolonged. During the period 1928 to 1931, 7 cases of post-vaccinal paralysis occurred, and these all terminated fatally. The treatment employed up to the date of occurrence of the 5th death was a modification of the method of Högyes. [From papers furnished to the Paris Conference the modification is described as follows: Cords are preserved in glycerine for a week, and are then made up with physiological saline in dilutions of 1/280, 1/240, 1/200, 1/160, 1/120. These are administered according to various schemes of dosage over periods varying from 15 to 21 days]. Thereafter vaccines killed by phenol were employed, but a further case occurred with the same characteristics of an acute myelitis as its predecessors and also terminated fatally. That the vaccine was killed, was shown by the fact that subdural inoculation did not infect the rabbit.

In three cases an autopsy was carried out, and from these the authors state that " many experiments on rabbits and monkeys were performed. The emulsions have been injected without result under the dura mater, into the muscles and under the skin." After excluding the possibility of either fixed virus or street virus being the causative agent, the authors fall back upon a toxin. [The time relations of the various fatal cases appear to us to be of importance. They are as follows :—

	Age.	Period of treatment.	Date of death.
1.	30	21.3.1928 to 10.4.1928	23.4.1928
2.	15	14.11.1928 to 4.12.1928	5.12.1928
3.	12	18.12.1928 to 7.1.1929	10.1.1929
4.	35	17.1.1929 to 2.2.1929	1.2.1929 (?)
5.	12	21.1.1929 to 7.2.1929	11.2.1929
6.	35	22.1.1929 to 11.2.1929	14.2.1929
7.	13	Nil	13.5.1929 (only Antitetanic serum given.)
8.	17	19.1.1931 to 8.2.1931	10.2.1931

Thus 5 of the deaths of treated persons occurred within the period of three months from December 1928 to February 1929, and in fact three of the persons who died were under treatment at the same time. The probability on the basis of pure chance that in one period of three months five deaths should occur, whilst in eighty previous periods during which the same method of treatment was employed, only one fatal accident was observed, is of the order of 1 in 10,000,000. It would thus appear that some unusual factor had come into operation during the period in question].

The effects of the injection of normal brain substance into rabbits and their bearing on the aetiology of paralytic accidents have been

[30] MOFTAH (S. G.) & NABIH (M. S.). Sur 21 cas de paralysie rabique.—*Bull. Office Internat. d'Hyg. Publique.* 1931. Nov. Vol. 23. No. 11. pp. 2007–2016.

studied by HURST.[31] In his experiments suspensions of foreign brain material of guineapigs (5), sheep (5), human beings (15), and monkeys (20) were employed. These were either untreated, or modified by moderate heating, or by carbolic acid. Dosage varied within wide limits. Certain of the animals died of an obvious infection, others (the majority of the fatal cases) died without any important microscopical lesions, and a smaller group of four died with symptoms of paralyses. In the latter group "no lesions of any degree could be found; in every case the vertebral column was normal, and despite the most diligent search no cause for a paralysis, in one instance preceding death by 5 days, could be determined." Two rabbits injected for other purposes with haemolytic sera developed precisely similar symptoms, and were killed after 9 days. Again no histological condition accounting for the paralysis was found. "From this experience it seems extremely improbable that in our own cases the nervous trouble was directly attributable to the brain substance injected." The author concludes that the parenteral introduction of such brain emulsions into rabbits causes severe toxic manifestations leading to wasting and death, but that there is insufficient evidence to warrant the view that the paralytic accidents of antirabic treatment are directly due to the foreign nervous substances injected. "There are good grounds for believing that in many cases the human lesions in cases of paralytic accident are identical with those of the disseminated encephalo-myelitis following the exanthemata, in which event it can hardly be held that the brain injections (or, as the case may be, the viruses of vaccinia, etc.) do more than stimulate into activity some latent factor or factors which are truly responsible for the nervous disability. Even if, as statistical evidence seems to show, paralytic accidents are a function of the quantity of brain substance administered, this may only mean that the activation of the second factor is favoured by a greater degree of toxaemia."

Three cases of persons treated by Adelheim's method (2 cc. daily of a 3–4 per cent. emulsion of cord dried for 24 hours) each of which showed a local erythematous reaction at the site of inoculation and each of which received treatment on subsequent occasions, are described by KAKTINE.[32] The first case was inoculated in 1902, 1908, 1914, 1916, 1920 and 1925; with each treatment the reaction became progressively weaker. The second was treated in 1923, 1924, 1926, 1927 and 1930 and showed a similar weakening of reaction. The third treated in 1922, 1923 and 1926 showed the same phenomenon.

vi. *Rabies in Animals.*

REMLINGER, MANOUÉLIAN and BAILLY[33] in continuation of an earlier research (this *Bulletin*, Vol. 27, p. 252) now show that street virus inoculated into the brain of the tortoise (*Testudo mauritanica*) may lie dormant without causing any symptoms in the animal for a longer period than the 110 days previously observed. In the case

[31] HURST (E. Weston). The Effects of the Injection of Normal Brain Emulsion into Rabbits, with Special Reference to the Aetiology of the Paralytic Accidents of Antirabic Treatment.—*Jl. Hygiene.* 1932. Jan. Vol. 32. No. 1. pp. 33–43. [35 refs.]

[32] KAKTINE (A.). Traitement antirabique réitéré et réactions locales.—*C. R. Soc. Biol.* 1931. Nov. 20. Vol. 108. No. 33. pp. 735–737.

[33] REMLINGER, MANOUÉLIAN & BAILLY. Recherches sur les centres nerveux de la tortue inoculée de virus rabique.—*C. R. Acad. Sci.* 1931. Nov. 30. Vol. 193. No. 22. pp. 1122–1124.

of three experiments, the brain was infective after 207, 163, and 163 days respectively. Subpassage into rabbits (two from each) induced symptoms in from 9 to 11 days. In every case Negri bodies were found in the nervous system.

A statistical summary of the results of preventive inoculation of dogs in seven prefectures in Japan since 1916 is given by Shinkichi UMENO and Sanae UMENO.[34] The methods employed have been variously those (1) of OSHIDA (1 part of fixed virus rabbit brain substance in 10 parts of 0·5 per cent. phenolated glycerine water), (2) of KONDO (1 part of brain substance from dogs infected with rabbit fixed virus in 6 parts of 0·5 per cent. phenolated glycerine water, incubated for 3 days), and (3) that of UMENO (1 part fixed virus rabbit brain substance in 6 parts of 0·5 per cent. phenolated glycerine water incubated for 3 days). The continued figures relating to the seven prefectures are as follows :—

Results of the Rabies Preventive Inoculations on Dogs in Seven Prefectures.

		Rabic dogs among			
	No. of dogs inoculated.	Inoculated.	Non-inoculated.	Stray dogs.	Total.
1916	—	—	326	277	603
1917	823	—	394	248	642
1918	8,500	—	452	314	766
1919	33,999	15	253	294	562
1920	27,043	4	150	213	367
1921	46,216	17	266	242	525
1922	33,830	20	185	122	327
1923	35,215	9	116	92	217
1924	47,449	43	481	509	1,033
1925	95,458	49	757	574	1,380
1926	102,677	32	437	369	838
1927	99,169	24	217	165	406
1928	97,597	15	47	36	98
1929	69,981	3	7	6	16
Total ...	697,957	231	4,088	3,461	7,780

Notes.—The figures are based upon the reports of the several prefectures under the survey.

The incidence of rabies among the inoculated dogs is 0·033 per cent., and of stray dogs is undeterminable.

It is stated that the high numbers of rabid dogs during the years 1924 and 1925 were due to the fact that on account of the earthquake in September 1923 the inoculations were not effectively carried out. The authors consider that " complete prevention of rabies lies in prophylactic inoculations of dogs which are the source of infection." Such measures must be generally applied, as adverse conditions prevailing in any one prefecture may profoundly influence its neighbours.

[34] UMENO (Shinkichi) & UMENO (Sanae). Results of the Rabies Preventive Inoculations on Dogs in Japan.—*Kitasato Arch. Experim. Med.* 1931. May. Vol. 8. No. 2. pp. 174–188.

AUJESZKY[35] reports that antirabic inoculation of dogs has been compulsory in Hungary since 1929. Of 5,344 dogs inoculated at Budapest, 29 have been killed or died of intercurrent disease. Of the remaining 5,315, one has died of rabies in spite of the vaccination. No case of rabies has resulted from the treatment. One case of post-vaccinal paralysis of a temporary nature was observed.

vii. *Miscellaneous.*

As cases of typhus fever, showing marked bulbar symptoms early in the disease, may simulate rabies and cause errors in clinical diagnosis, STUART and KRIKORIAN,[36] at the instance of the Colonial Medical Research Committee, have carried out an investigation on the serological relationship between the two diseases, and in particular have subjected the sera of rabies subjects to the Weil-Felix reaction. The results which they have obtained from laboratory investigations made into typhus and rabies infections in man and in experimental animals prove a complete absence of serological relationship between the two diseases. In no case did the serum of the typhus subject exhibit any rabicidal property. On the other hand, the sera of four hydrophobia cases, two treated and two untreated, possessed no significant X 19 agglutinins, and the sera of 30 guineapigs and 30 rabbits which had been infected with rabies did not agglutinate X 19 strains even in 1 in 10 dilution.

In a short note PLANTUREUX[37] states that five dogs vaccinated against rabies, 3 before and 2 after splenectomy, have all exhibited a strong immunity. The presence of the spleen does not therefore appear to be necessary for the establishment or the conservation of antirabic immunity.

From a series of experiments on 42 dogs and a number of rabbits REMLINGER and BAILLY[38] conclude that there is no truth in the proverb that the badly nourished dog is sheltered from rabies—"le chien mal nourri est a l'abri de la rage." The behaviour of the virus in cachectic animals is identical with that observed in animals in perfect health.

From a further series of experiments these authors[39] conclude that anaesthesia by chloroform or ether (4 administrations, each of 30 minutes duration) is without influence on the incubation period of rabies.

In an article entitled "Studies on Rabies" REMLINGER and BAILLY[40] have collected a number of papers from the *C. R. Soc. Biol.*

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35 AUJESZKY (A.). Vaccination antirabique des animaux domestiques en 1929.—*Allatorvosi Capok.* 1931. No. 6. p. 67. [Summarized in *Bull. Inst. Pasteur.* 1932. Feb. 29. Vol. 30. No. 4. p. 220.]

36 STUART (G.) & KRIKORIAN (K. S.). Rabies *v.* Typhus.—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. Mar. 31. Vol. 25. No. 5. pp. 353–366. [22 refs.]

37 PLANTUREUX (E.). Immunité antirabique et splénectomie.—*C. R. Soc. Biol.* 1932. Mar. 4. Vol. 109. No. 8. p. 632.

38 REMLINGER (P.) & BAILLY (J.). L'état d'entretien d'un animal est sans influence sur la pathogénie de la rage.—*C. R. Soc. Biol.* 1932. Apr. 15. Vol. 109. No. 12. pp. 1074–1076.

39 REMLINGER (P.) & BAILLY (J.). Rage et anesthésie.—*C. R. Soc. Biol.* 1932. Apr. 29. Vol. 109. No. 14. pp. 1241–1242.

40 REMLINGER (P.) & BAILLY (J.). Etudes sur la rage. (Premier mémoire.)—*Ann. Inst. Pasteur.* 1931. Dec. Vol. 47. No. 6. pp. 608–659. [Refs. in footnotes.]

which have already been reviewed, viz.: (1) Presence of virus in the spleen, liver and kidney (this *Bulletin*, Vol. 28, p. 742); (2) Existence of avirulent regions in the central nervous system (Vol. 28, p. 744); (3) Plurality of fixed virus strains. All are not inoffensive to man (Vol. 29, p. 190); (4) The toad and the frog are refractory to rabies (Vol. 28, p. 254); (5) Passage of fixed virus into the central nervous system of vaccinated animals (Vol. 28, p. 745); (6) Does normal brain substance sensitize rabbits to the virus of rabies? and dilution methods of treatment (Vol. 29, p. 192); (7) The identity of Mal de Caderas with rabies (Vol. 29, p. 189); (8) The repetition of pasteurian treatment does not induce anaphylaxis (Vol. 28, p. 747).

A. G. McKendrick.

PLANTUREUX (E.). Sur le traitement des herbivores après morsure par le vaccin antirabique formolé.—*Arch. Inst. Pasteur d'Algérie.* 1931. Sept. Vol. 9. No. 3. pp. 490–493. [Reviewed in this *Bulletin*, Vol. 29, p. 195.]

BERIBERI AND EPIDEMIC DROPSY.

BERNARD (P. Noel). Recherches sur le béribéri. [**Research on Beriberi.**]—*Ann. Inst. Pasteur.* 1931. Nov. Vol. 47. No. 5. pp. 508–578. With 11 text figs. & 4 figs. (2 coloured) on 2 plates. [Refs. in footnotes.]

The first part of this very long and elaborate paper contains an historical account of the various theories concerning beriberi etiology. The second section presents the thesis that the disease shows all the manifestations characteristic of a toxi-infection. It is important to realize that beriberi in Indo-China appears both in isolated sporadic cases and in true epidemics ; also that the disease should rationally be divided into the types—acute, subacute, chronic and *formes frustes*. During epidemics (for example, that described in Tanan, Cochin-China, 1927–1928) certain interesting features were noted, such as the contagious nature of the disease ; the liability of all members of the community, and not only the very poor, to attack ; all live in the open air and feed as they like ; no children under 10 nor adults over 50 are affected ; in 1928 out of 127 cases admitted to hospital 10 died suddenly from the acute pernicious form of the disease. It is argued that only such acute cases should be employed as material for etiological research since they are usually young, robust, well-nourished subjects and have no complicating picture of debilitating disease.

Considering the importance of such acute cases the following clinical description may be noted. The patient presents the appearance of an acute febrile illness with constipation, severe tachycardia, praecordial pain, diminished urine secretion and acute distress. Death may occur in a few hours ; sometimes this is delayed for a day or two or even a week, and occasionally may occur later still during a relapse. If the patient recovers from the acute attack peripheral neuritis, with or without oedema, appears. Thus possibly months later the picture of beriberi too often regarded as typical is presented. Those observers who identify human beriberi with experimental B-avitaminosis have taken the more chronic forms as their type and consider the absence of fever and albuminuria to be essential. In the acute pernicious form of the disease, however, fever is present and the urine contains albumin and casts.

The third section of the paper deals with the relationship between human beriberi and experimental toxi-infection. The experimental animal of choice was the young pig and the infective agent B. asthenogenes. This organism is found in various foods, especially rice, and becomes pathogenic in the digestive tract and there produces a toxin which gives rise to a definite clinico-pathological picture. When the animals are given cultures of B. asthenogenes only a half of them, or less, contract the disease and the symptoms vary from a simple febrile gastritis with constipation, myalgia, asthenia and temporary pareses up to death in a few days or a polyneuritis syndrome. In human subjects suffering from a febrile gastro-enteritis the bacillus has been found in blood cultures and the condition of the patients has progressed to the state met with in experimentally infected pigs. It is important to note that blood cultures are only positive during the febrile stage, showing that the septicaemia is not permanent. In the pig, following ingestion of the organism or its filtered toxin the

post-mortem changes in the heart and other organs are identical with those found in human beriberi and it seems incontestable that these changes are of a toxic order.

Many other important points emerge from the experimental work on young pigs. (1) The experimental disease does not appear in animals fed with rice of which all the vitamins have been destroyed by heat unless the bacillus is also present. (2) The presence of vitamins is not sufficient to protect animals against the experimental disease but avitaminosis favours its development. (3) The experimental disease is transmitted from diseased to healthy animals by contact with infective faeces and urine. (4) Laboratory diagnosis is uncertain since the organism is present in the excreta of control animals and complement-fixation tests give varying results both in the animal and in man. (5) The first phase of the disease consists in fermentation of the stomach contents and the gastro-duodenitis of human beriberi is exactly comparable, both macro- and microscopically, with the changes found in the experimental animal.

There follows a detailed description of the bacillus and its toxin which is of too technical a character for discussion.

In conclusion the author stresses the following points: True beriberi is an acute disease and the usual type described is not true beriberi at all, but only a sequel of a previously contracted toxi-infection. It is not due to the invasion of a specific organism but the toxi-infective phenomena of the disease develop on a soil already prepared by a badly balanced diet in which carbohydrates are in excess and other elements insufficient. Three factors, then, are necessary for the production of the disease—the toxin-producing organism, a gastro-intestinal condition favouring its action and a lowered resistance resulting from a faulty diet. If one of these factors is lacking, even though the other two are present, beriberi does not make its appearance.

[This is a very long and valuable paper and it is impossible in a short abstract to do it justice. Those interested will be amply repaid by reading the original.] *A. D. Bigland.*

NGUYEN-VAN-KHAI. Contribution à l'étude clinique du béribéri en Cochinchine. [**Beriberi in Cochin-China.**]—*Bull Soc. Méd.-Chirurg. Indochine.* 1932. Jan. Vol. 10. No. 1. pp. 18–63.

The author has an extensive and intimate knowledge of beriberi in Cochin-China and here records his clinical experience of more than twenty years. Only the more important findings need be discussed.

Beriberi is a toxi-infective disease having two definite stages (1) the invasion period characterized by fever, pain in the back and digestive disturbances. This lasts some days and is often overlooked. (2) The period of polyneuritis, with or without oedema, and cardiac symptoms of varying gravity. Since the toxin may affect either the motor, sensory, sympathetic or pneumogastric nerves or a selection of these, it follows that the clinical picture will be a very varied one.

The paralysis is of the flaccid type without sphincter involvement and later progressive wasting may manifest itself even to the extent of "main en griffe." Albuminuria is as a rule absent except in very grave cases. Constipation is frequently found. The knee jerks are first exaggerated and later disappear. Absent knee jerks may persist for a long time and in four cases this was found some 10 years after complete cure of the disease. Alterations in the voice are constant and dysphagia may be present in severe cases.

In addition to the classical types of beriberi two more varieties are described. (1) A chronic form. This is characterized by slow onset so that the patient does not come under observation for 2–3 months or even longer. As the disease progresses motor and sensory disturbances appear first in the legs, then in the arms. The heart is slightly or not at all affected, the knee jerks are always absent and the general health is satisfactory. Apparently the patient may remain in this condition for years. (2) A residual form in which certain nervous symptoms persist after cure of the active disease.

Another type of the disease is known as post-partum beriberi. This generally appears 1 week to 2 months after parturition and in some women follows each successive birth. Infantile beriberi occurs only in babies who are suckled by mothers suffering from the disease.

In the section dealing with diagnosis mention is made of the inability of beriberi patients to raise the thighs and legs in a straight line when lying on their backs and to sit up without the aid of the arms. Complement deviation tests with B. asthenogenes, chloride retention and hypoglycaemia may be of diagnostic assistance.

Beriberi is apparently on the increase in Cochin-China but accurate statistics are difficult to obtain. At one prison in 1924 there was a morbidity of 32 per cent. with a mortality of 18 per cent., and in another epidemic occurring in a certain plantation a morbidity of 36 per cent. was recorded and one-third of those attacked died.

A. D. B.

PLACIDI (Th.). Note au sujet du "béribéri." [**Note on Beriberi.**]—*Rev. Méd. et Hyg. Trop.* 1932. Mar.–Apr. Vol. 24. No. 2. pp. 67–69.

Two epidemics seen in the New Hebrides are briefly described. On one plantation where Kanakas and Annamites lived side by side without beriberi the disease appeared soon after the arrival from Indo-China of a convoy of labourers, three cases among the Annamites and four amongst the Kanakas.

On another plantation were villages of 250 newly-arrived Chinese and 95 Annamites, for reasons of discipline kept strictly apart. Beriberi (65 cases) appeared among the Chinese, interrelation was perforce recognized and soon after four cases were found among the Annamites who had been free from beriberi for several years.

The author finds it difficult to attribute these outbreaks to avitaminosis. He gives the ration and says it was supplemented from the gardens. The use of decorticated rice is general in the Archipelago and the same rice was eaten in these as in neighbouring plantations. He would attribute the outbreaks to infection and thinks the disease was introduced in each case from Asia. Few details are given.

A. G. B.

ALBERT (José). **Studies on Infantile Beriberi based on Five Hundred Fourteen Cases.**—*Philippine Jl. Sci.* 1931. June. Vol. 45. No. 2. pp. 297–319. With 1 text fig. [32 refs.]

Infantile beriberi, the disease which affects babies suckled by mothers who are themselves sufferers, is a terrible scourge in the Philippines, claiming an average of 16,500 deaths annually (28·10 per cent. of the total deaths among infants under one year of age).

The disease must not be regarded as adult beriberi in miniature for it differs "in almost every particular; pathological, clinical and therapeutical." The chief symptoms are obstinate vomiting, incessant crying, dyspnoea, oedema, aphonia, lessened urine secretion and tachycardia. Multiple peripheral neuritis does not occur. Among the etiological factors the following may be noted:—The disease occurs most often during the rainy season; it is never observed in Caucasians and only rarely in white half-breeds; the most dangerous age period is 1–3 months; both sexes are about equally affected; it is strikingly a disease of poverty and apparently does not occur in infants who were never breast fed. In the few cases recorded of the disease in artificially fed infants breast feeding at some period was usually found.

In analysing the causal relationship between infantile beriberi and mothers' milk the following points are of interest: (1) The severity of the disease in the child is not directly proportional to the severity of the disease in the mother. (2) Children of mothers presenting no objective or subjective symptoms of the disease are affected. About 25 per cent. of cases belong to this group. The onset of the disease in the child may precede that in the mother. (3) Infantile beriberi is independent of the duration of breast feeding. In one of the author's cases a baby had only been on the breast one week before the institution of artificial feeding.

As a result of GUERRERO's work (1904) and the therapeutic discovery of CHAMBERLAIN and VEDDER (1912) "this implacable and wanton enemy of breast-fed babies is now wane-ward bound." In 1906 the infant mortality rate for the City of Manila was 476·17, whereas in 1930 it was only 160·24; "this diminution is due mainly to the reduction in the mortality from infantile beriberi, which, without the least shadow of doubt, has been successfully fought by tikitiki."

A. D. B.

BRENNAN (T. J.). **The Early Diagnosis of Beriberi.**—*Jl. Philippine Islands Med. Assoc.* 1931. Dec. Vol. 11. No. 12. pp. 482–483.

The author maintains that incipient beriberi is inadequately described in the text books. There are, he says, five subjective symptoms, found in over 90 per cent. of these cases: "(1) Upper chest pain, either back or front or both; (2) Insomnia; (3) Palpitation; (4) Pain or numbness of legs; (5) Fatigue after slight exertion."

Such persons do not consider themselves sick. Physical examination shows only slight muscular weakness and tenderness, some anaesthesia over the shins, tachycardia and increased or decreased knee jerk. If rice is omitted from the diet and a teaspoonful of tikitiki is given three times a day, the symptoms will disappear in 7–10 days.

A. G. B.

VAN VEEN (A. G.). **Concerning Anti-Beri-Beri Vitamin Preparations.**—*Meded. Dienst d. Volksgezondheid in Nederl.-Indië.* 1931. Vol. 20. Pt. 2. pp. 73–79.

The following is an account of the changes in composition and application found necessary in the various anti-beriberi vitamin preparations issued by the medical laboratory at Weltevreden.

Vitamin tablets and powder.—According to JANSEN and DONATH 4 tablets (1 gram of the powder) correspond to 30 grams of rice bran, which is about the daily quantity of anti-neuritic vitamin needed by an adult (0·5 mgm. of vitamin). During the last two years repeated tests on birds showed that in about one-third of the samples a lowering of the vitamin content occurred so that 6 tablets, or 1·5 gm. of powder, had to be given for a daily dose. Owing to the low selling price of the preparations this defect is likely to continue. The poor disintegrating power of the tablets, which was troublesome at first, has been overcome by the simple addition of a little starch.

The activated clay contains in addition to vitamin, a large amount of organic substances adsorbed from rice bran. The majority of these cannot be removed by chemical means but it seems probable that the alimentary tract is able to perform this separation.

Extract of activated clay.—0·2 cc. of this extract is equivalent to 4 tablets, or 0·5 mgm., of vitamin. Here again many other organic substances are present and the slightly acid extract is an excellent feeding ground for moulds and bacteria. Alcohol has been found to be a better preservative than either toluene or glycerol.

Ampoules.—Originally each of these contained 2 cc. of liquid in which 1 mgm. of anti-neuritic vitamin and 3 mgm. of other substances were dissolved. It was found that toxic effects of a serious nature sometimes followed injection and that the vitamin content of each ampoule was apt to be only one-half of that specified. Successful attempts have been made to remove the toxic substances and it is hoped soon to perfect a method of increasing the vitamin content. As acute beriberi is rare in the Dutch East Indies hypodermic medication is not of great importance.

In conclusion the author records his experience with other anti-beriberi vitamin preparations.

Metatone (Parke, Davis and Co.).—The dose is stated to be 1–2 teaspoonsful, but even 25 cc. given with the food did not protect birds against polyneuritis.

Oryzanin tablets.—The prescribed dose is 12 tablets per diem but 15 were found necessary to protect test birds.

Oryzanin extract.—Prescribed human dose is 9 gm. per diem, but not less than 15 gm. was found adequate for birds.

Liquid Oryzanin.—A daily dose of 20 cc. added to the birds' food was sufficient protection.

Oryzanin Ampoules.—According to a previous report 4 of these ampoules was sufficient but in another series a dose of 3 ampoules was ineffective and a mouse injected intravenously with $\frac{1}{3}$ cc. died immediately.

Eviunis. (Obtained from Prof. WENCKEBACH).—A dose of 4 gm. *per diem* of this powder was found adequate in bird tests. *A. D. B.*

TOURNIER. Les éléments de la thérapeutique du béribéri. [**The Treatment of Beriberi.**]—*Ann. de Méd. et de Pharm. Colon.* 1931. Oct.–Nov.–Dec. Vol. 29. No. 4. pp. 861–871. [27 refs.]

This very full account of various therapeutic measures employed in beriberi may be summarized as follows :—

Antitoxic Treatment.—This consists of (1) the exclusion of rice or other decorticated cereal from the diet. (2) Giving a fresh milk diet to acute cases and a lacto-vegetarian diet to sub-acute and chronic

cases. (3) Elimination of toxins by blood letting (at least 300 cc. at a time) with or without blood transfusion ; by exhibition of saline purgatives (especially magnesium sulphate), diuretics and calcium salts (especially the gluconate). (4) Correcting acidosis by small doses of insulin, in conjunction with intravenous injections of glucose. Insulin is contra-indicated in under-nourished subjects. Other remedies to be tried under this heading are sodium bicarbonate, glucose, and organic extracts, such as adrenaline, thyroid and liver.

Anti-Infection Treatment.—(1) By the use of general antiseptics such as iodine, colloidal metals and arsenic. (2) Gastro-intestinal antiseptics—urotropine, sodium benzoate and sodium salicylate. These are especially recommended by those who regard the starting point of beriberi as a specific infective gastro-duodenitis. (3) Anti-parasitic medication (e.g. quinine and anthelmintics), since infections like malaria and ankylostomiasis seem to favour the development of beriberi. (4) Saline purgatives.

Symptomatic Treatment.—(1) *Cardiac tonics.*—The author, contrary to some workers' experiences, has not seen any good result follow the use of digitaline and ouabaïne in acute cases. Caffein, camphor in oil and spartein are preferred. (2) *Diuretics.*—Digitalis, caffein and glucose have already been discussed. Theobromine was found to be without action in acute cases. According to WINCKEBACH and AALSMEER, novasurol, salyrgan and neptal are also of no value. Calcium chloride appears to be indicated especially when oedema and albuminuria are present, and possibly to increase the effect of the mercurial diuretics. Glucose and lactose solutions are useful when hypoglycaemia and under-nourishment are present. (3) *Nervous system tonics.*—These are particularly useful in the "dry" form of beriberi. Strychnine holds first place but should not be used in acute cases. Such drugs as kola, quinine, arsenic and iron, though used extensively in Indochina, have not given appreciable results. Electrical treatment may be of value in some cases. (4) *Opotherapy.*—In this category adrenaline, particularly in acute cases, is the most important. Thyroid extract in small doses (sometimes combined with hypodermic injections of a 5 per cent. oily solution of cholesterine) has been recommended but in Indochina it was found to have no effect in altering the evolution of the disease though the general condition of the patient was improved. Pituitary, gastric, intestinal and liver extracts (especially the last) are useful adjuvants to other forms of treatment. (5) *Vago-Sympathetic Treatment.*—Atropine and ephedrine are useful drugs during the acute stage of beriberi. (6) *Vitamins and Amino Acids.*—For those who regard beriberi as a deficiency disease a protein-rich diet and vitamin B preparations are essential. *A. D. B.*

AALSMEER (W. C.). Enkele waarnemingen bij de behandeling van lijders aan beri-beri. [**Some Observations in the Treatment of Beriberi.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1932. Feb. 15. Vol. 72. No. 4. pp. 206–212.

The various symptoms of beriberi reach their height during different stages of the disease. The author, whose views on this subject have been previously referred to (see this *Bulletin*, Vol. 28, p. 460), attaches most value to the condition of the circulatory apparatus, and especially to the minimal blood pressure. He found adrenalin exerts a dilating

influence on the vessels in beriberi, thereby lowering the minimal blood pressure for a while. By means of this test a number of patients were studied under various courses of treatment, and the therapeutic action of single measures thus estimated. Rest may have a beneficial influence but does not cure the condition so long as no extra vitamins are administered. Unpolished rice and katjang idjau are both useful in this respect. The same effect is obtained by injections of purified antineuritic vitamin (JANSEN & DONATH). Failure of the usual treatment may sometimes be ascribed to unsatisfactory absorption of vitamins from the intestine or to disturbance of their assimilation. The author thinks that his experiments lend valuable support to the deficiency theory of beriberi. *W. J. Bais.*

AYKROYD (W. R.). **The Effect of Parboiling and Milling on the Antineuritic Vitamin (B_1) and Phosphate Content of Rice.**—*Jl. Hygiene.* 1932. Apr. Vol. 32. No. 2. pp. 184–192. [Summary appears also in *Bulletin of Hygiene.*]

The parboiling of rice is usually carried out by soaking unhusked grains in water for 24–36 hours, steaming them for 15–20 minutes and finally drying them in the sun; the husk can then be separated from the grain with comparative ease. It has been observed that beriberi does not occur in people who habitually eat parboiled rice and the explanation has been advanced that parboiled rice contains more vitamin B_1 than polished rice because less of the husk is removed. Experiments were carried out with young rats to determine the respective vitamin B_1 contents of different samples of the same rice (a) milled raw, (b) milled to exactly the same extent after parboiling. Much larger amounts of vitamin B_1 were found in the milled parboiled rice than in the milled raw samples. On the other hand the millings from the raw rice contained more vitamin B_1 than the millings from parboiled rice. It appears that during the process of parboiling vitamin B_1 is washed into the endosperm from the pericarp. Similarly larger amounts of phosphate were found in milled parboiled grains than in milled raw grains, but less phosphate in the millings from the parboiled rice than in those from raw rice. The phosphate content of raw rice is usually a good index of its vitamin B_1 content, but parboiled rice may have a comparatively low phosphate content and a high vitamin B_1 content. *S. J. Cowell.*

OHMORI (Kenta), OKAMOTO (Hisata), HARA (Minoru), NAKAMURA (Soji) & KUROKAWA (Kiyoyuki). Studien über das sogenannte Oryzatoxin als Ursache der Beriberi-Krankheit. [**Oryzatoxin as the Cause of Beriberi.**]—*Kitasato Arch. Experim. Med.* 1931. Oct. Vol. 8. No. 4. pp. 315–340. With 4 figs. on 1 plate. [14 refs.]

Some workers have found that alcoholic extract of polished rice when fed to birds and mice caused hardly any symptoms, but when injected weakness and death soon followed. Others, however, repeating these experiments with rabbits found that in the preliminary test the animals died soon after injection but in the test proper no untoward symptoms occurred. Similar tests with fowls showed temporary paralysis only after repeated injections, though the animals lost weight and died. This resulting paralysis was not cured by injection

of oryzanin. It seems, therefore, that a poisonous substance may exist in alcoholic extracts of polished rice which only becomes evident when administered subcutaneously.

In order to prove or disprove the presence of this so-called oryzatoxin the authors of the present paper also conducted experiments, using a cold alcoholic extract of polished rice and feeding fowls upon the residual rice flour. The following are amongst the results :—(1) Animals fed upon extracted and non-extracted rice showed exactly similar clinical and pathological findings. (2) Adding oryzanin or ebios to the previously extracted rice kept the animals well and healthy. (3) When animals living on polished rice are fed or injected with alcoholic extract of rice symptoms of paralysis occur but oddly enough later than in animals not so treated, and in each case when the disease does occur it is identical. (4) In animals compulsorily fed upon polished rice there was no difference in the incubation period of injected and non-injected specimens. (5) In a few cases, however, slight paralysis followed a single injection of oryzatoxin. But in no case was any paralysis noted when an adequate supply of vitamin B was present in the diet.

The authors conclude that a toxic substance probably does exist in cold alcoholic extracts of polished rice but the experimental results vary and, therefore, no definite conclusions can be drawn. *A. D. B.*

SHANKS (G.) & DE (M. N.). **The Pathology of Epidemic Dropsy.**—*Indian Jl. Med. Res.* 1931. Oct. Vol. 19. No. 2. pp. 469–474. With 13 figs. (4 coloured) on 5 plates.

A considerable amount has been written during the past 20 years or more on the subject of epidemic dropsy, but almost entirely from the aetiological, epidemiological and clinical aspects, and with what appears to be a preconceived idea of its close connexion with wet beriberi. This conception is probably responsible to a large extent for burking enquiry and hindering research. More recently evidence has been accumulating in favour of the condition being a distinct morbid entity and this paper, describing almost for the first time the morbid anatomy and histology, will do much to stimulate research, which to be productive should be taken up *de novo*.

The authors describe the detailed findings of 4 fatal cases, all adults, 3 males of 40, 52 and 35 years, and 1 female of 31 years. The female and one male were Hindus, one an Anglo-Indian and one a Mohammedan. Unfortunately in two of the cases the necropsy was not held until the lapse of an interval (28 and 43 hours) after death which would render microscopical examination of tissues valueless in a tropical country. The gross changes were the anasarca in all, hydrothorax in three, ascites in two, hydropericardium in one and the fluid in this bloodstained ; petechiae or dilated vessels recognizable by naked eye were present in all and multiple " angiomata " in one ; the adrenals were " mushy " in one patient, not noticeably altered in the others. In each case the patient had been ill for about a month before coming to hospital and death occurred in less than 5 weeks from the onset in the first, in 5, 6, and between 7 and 8 weeks in the others.

The most striking lesion microscopically was dilatation of capillaries, most marked in parts where they were poorly supported, the fatty tissue of skin, pericardium, peritoneum, spinal meninges, etc. These

are shown in some excellent photographs, but better still in the coloured plate. The authors state that the "haemorrhagic-looking areas" were not due to extravasations of blood but to extreme vascular dilatation; nevertheless in some places these had ruptured.

[The indications are rather those of some general toxin acting upon endothelium and examination of further tissues in as fresh a state as possible may reveal small haemorrhages by diapedesis such as are found in conditions due to phytotoxins, the symptoms seem to be too drawn out for glucoside or saponin action, or poisons of the ricin, crotin, abrin group, but they might arise from the slower action and cumulative effect of a food *poison*, some fungus or plant (rather than a food *deficiency*) analogous to lathyrus on the central nervous system, and claviceps on the vessels, in other words a circulating toxin producing a purpuric condition--a symptomatic purpura, i.e., purpura of unelucidated aetiology. No emigration of leucocytes was seen, but diapedesis can occur without this. Patient No. 2 who presented widespread nodular lesions of an "angiomatous" character would have been the best subject for this examination, as the post-mortem was carried out only 6 hours after death, but in this case "unfortunately the material was not available for microscopical study." It would be well to avoid the term angioma, for this implies a more or less independent growth of vessels, often not communicating with the capillaries of adjacent tissue; it differs from mere dilatation such as is described in epidemic dropsy.] *H. H. S.*

BUCHANAN (J. C. R.). **"Chachaleh," a Common Disease in British Somaliland, and its Relation to Tropical Deficiency Diseases.** — *Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. Mar. 31. Vol. 25. No. 5. pp. 383–397. [14 refs.]

In British Somaliland there occurs a somewhat ill-defined disease characterized by pain in the muscles, bones and joints; "burning feet" and other paraesthesiae; and varying degrees of oedema. This condition is called by the natives "Chachaleh" and "Barasheh."

The clinical features analysed from 100 cases, are as follows:--It is a very chronic condition and may last 10 years with only slight disability. It is seldom, if ever, fatal. Pain is usually generalized but may occur in various localities, particularly in the joints and at the back of the neck and shoulders. 82 per cent. of the patients showed oedema of varying degree, while there was thickening of the subcutaneous tissues (especially in the thighs, abdomen, pectoral and deltoid areas) in 41 per cent. The knee jerks tend to be diminished and the symptom "burning feet" was recorded in 39 cases. Epigastric pain was common and constipation the rule. In only 15 cases was myocardial weakness present and then only in a minor degree. In 3 cases there was severe cardiac involvement. Some fever was present of a low intermittent type. The urine was normal.

Treatment, of sufficient duration to be of value, was carried out in 50 cases. (1) 22 patients received tincture of iodine in increasing doses of 10–25 minims in 4–8 cc. distilled water intravenously twice weekly. Of these 13 were improved and 6 cured. (2) 17 cases received 1 oz. of yeast t.d.s. together with one uncooked onion. Of these 8 were improved and 6 cured. (3) A combination of the above treatment tried in 11 cases resulted in 6 being cured and 4 relieved. No alteration in the diet was advised and saline purgatives were given

as a routine procedure. It seems that the yeast and onion treatment was particularly effective in removing oedema and the iodine in dealing with pain and paraesthesiae.

In the section dealing with etiology, diets in Somaliland receive full consideration.

"These contain most of the essential elements but lack variety and balance; it is also doubtful if the vitamin content is always adequate, and their nature is such that it is questionable if foodstuffs ingested are fully absorbed and utilised by the body. In any case, the margin of safety is so small that a slight fall below the average will bring them within the danger zone of deficiency, and a fall will invariably affect animal protein and vitamins most, since hard times to a Somali mean that he consumes less milk and mutton than usual and supplements his diet with cheap rice."

The disease was found in all classes of natives, slightly more often in females, but those having a full and assured diet were relatively immune.

Chachaleh bears a resemblance to the ill-defined and "larval" types of beriberi, but its similarity to epidemic dropsy is so great that it is doubtful whether the two conditions can be separated. The symptom "burning feet" it will be remembered was common in the pellagra cases described by STANNUS [this *Bulletin*, Vol. 27, p. 766]. *A. D. B.*

AALSMEER (W. C.). Ueber den Einfluss des Adrenalins auf den diastolischen Blutdruck bei Aorteninsuffizienz und Morbus Basedowii in Analogie zur Beriberikrankheit.—*Klin. Woch.* 1932. Feb. 27. Vol. 11. No. 9. pp. 362–366.

HIZON (Rafael P.). Tiki-Tiki Extract in the Treatment of Adult Beriberi.—*Bull. San Juan de Dios Hosp. of Manila.* 1931. July. Vol. 5. No. 7. pp. 192–197. [14 refs.]

ROSEDALE (John Lewis) & OLIVEIRO (Christopher Joseph). Studies on the Antineuritic Vitamin. The Relationship of Beriberi to the B Vitamin Complex.—*Far Eastern Assoc. Trop. Med. Trans. Eighth Congress, Bangkok, 1930.* pp. 86–96. [12 refs.]

PELLAGRA.

FAKHRY (Asaad). **Incidence, Parasitological Findings and Treatment of Pellagra in Kafr-El-Zayat Ankylostoma Hospital, 1930.**—*Jl. Egyptian Med. Assoc.* 1932. Feb. Vol. 15. No. 2. pp. 53–64. With 3 graphs in text.

During 1930 at the Ankylostoma Hospital, Kafr-El-Zayat, pellagra occurred in 214 patients (1·22 per cent. of the total). The largest number of cases was found in April and the least in August. Males under 12 years were apparently particularly susceptible. Out of 175 pellagrins 162 (92·3 per cent.) showed by ordinary methods of examination ova of *Schistosoma haematobium* or *mansoni* or both; while the bilharziasis rate for the whole hospital was 68·6 per cent. In pellagra, intestinal bilharziasis was the commoner of the two infections and the incidence rate was nearly double the hospital average for all patients. It is suggested that such intestinal changes may cause either excessive destruction of proteins or their defective absorption and therefore may play a part in the causation of pellagra. A similarity between bilharziasis incidence in pellagrins and in cases showing only stomatitis tends to demonstrate that the latter may be a prodromal symptom of pellagra.

Satisfactory therapeutic results followed daily intravenous injections of 10 cc. of a 10 per cent. sodium thiosulphate solution. Children received only half this dose. It is suggested that the concentration of the thiosulphate solution should be increased to 33·3 per cent. so that the bulk of the injection may be reduced to 3 cc., thus facilitating routine treatment. On the assumption that stomatitis is an early symptom of pellagra such cases should also receive treatment.

[In the discussion which followed opinion seems to have been divided concerning the presence of stomatitis as an early symptom of pellagra.] *A. D. Bigland.*

KASSIRSKY (J.) & BUROVA (L.). Zur Klinik der Pellagra in Mittelasien. [**Pellagra in Tashkent.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1932. June. Vol. 36. No. 6. pp. 323–336.

Forty-eight cases of pellagra were observed in the Clinic for Tropical and Internal Diseases, Tashkent (Russian Turkestan). The following points seem worthy of notice:—

(1) Bacteriological examinations of the mouth were made in 26 cases showing sore tongue. All showed the presence of Vincent's fusiform bacilli and spirochaetes in large numbers.

(2) In a few cases after prolonged diarrhoea invagination of the intestine occurred as evidenced clinically by the presence of a palpable tumour with visible peristalsis. This invagination never reduced itself owing to subsequent inflammatory changes.

(3) Chemical examinations of the blood revealed a lessened cholesterin content and an increase of the potassium and calcium contents in 97 per cent. of cases.

(4) A few cases presented a diabetes insipidus syndrome.

(5) No marked anaemia was present though puncture showed changes in the bone marrow.

(6) The total blood quantity in serious pellagra cases fell even as low as 5·0 per cent. of the body weight (normal figure is 6·7–7·0 per cent.).

(7) A rich protein diet together with the administration of calcium chloride quickly relieved the diarrhoea but the other symptoms remained as before and even progressed. Small doses of thyroid extract and a vitamin-rich diet proved fairly successful. Blood transfusion gave only temporary improvement.

(8) The mortality figure was 28 per cent. and in the following spring 30 per cent. of the improved cases returned with a relapse.

A. D. B.

KLEINMANN (H.). Beiträge zur Frage der Pellagra mit besonderer Berücksichtigung der Pellagra in Moldavien. [**Pellagra in Moldavia.**]—*Arch. f. Dermat. u. Syph.* 1931. Nov. 19. Vol. 164. No. 2. pp. 393–398. [23 refs.]

In a hospital at Birsula, a town in Moldavia, 63 cases of pellagra were studied. The patients were collected from 28 different villages in the district; thus in 18 villages there was only one case in each, in 4 villages 2 cases and in 2 villages 5 cases. The greatest number of pellagrins in any one village was 13. This scattered distribution is rather remarkable in view of the fact that pellagra is very prevalent in the neighbouring area of Southern Ukraine.

All the patients were land workers and came from the very poorest class of the community. Apparently maize is a staple article of diet and it is sometimes mixed with wheat or barley flour. The remainder of the diet is made up of pickle soup, onions, pickled cucumbers and potatoes. Meat and milk are only occasionally consumed and alcohol never. Females are attacked in the proportion of 46 : 17 males. Nearly all the males were over 40 years of age, whereas in females every age period was equally liable to the disease. Members of the same family were rarely attacked except for two instances in which mother and daughter were victims, two instances in which two sisters were victims and in one family the father and two grown-up sons were found to be sufferers. The earliest cases (2) dated from 1920; in 1929 there were 17 cases; in 1930, 31 cases and in 1931, 5 cases.

In addition to the usual symptoms, hyperkeratosis of the nose-lip area was noted in 14 cases and in 20 cases there was the unusual feature of falling out of the outer part of the eyebrows. Vulvitis was common, and in 34 gastric examinations achlorhydria was present in 33.

The author considers that pellagra is not a vitamin deficiency disease but rather the expression of an endocrine-sympathetic disturbance resulting from the action of a toxic substance. He is of the opinion that the facial hyperkeratosis, the blood changes, the achlorhydria and the falling out of the eyebrows are symptoms of great differential diagnostic importance. *A. D. B.*

SPIES (Tom Douglas). **Pellagra and Vitamin Deficiency.**—*Proc. Soc. Experim. Biol. & Med.* 1931. Oct. Vol. 29. No. 1. pp. 83–86. With 2 text figs.

The author points out that in so many dietary experiments dealing with pellagra etiology adequate controls have not been used. To

remedy this defect four acute pellagrins (3 white males and 1 negress) were studied while receiving a 2,300 calorie diet consisting of: "corn meal mush, corn meal muffins, pork fat, maple syrup, polished rice (boiled), cornstarch pudding, coffee and sugar." It will be seen that this regimen is more restricted in mineral content and in vitamin C and B than was the classical pellagra-producing diet of GOLDBERGER. Striking and almost immediate improvement in all four cases was noted and there was no return of signs or symptoms during the 6–7 weeks' stay in hospital on this diet.

The three male patients had a history of alcoholism, while all presented on admission typical pellagra appearances and gave a history of dietary deficiency extending over two months or more.

[In view of the alcoholic history of the three male cases it can be argued that the stay in hospital with its consequent abstinence played an important part in their remarkable recovery.] *A. D. B.*

KAHN (Bernard L.). **Pellagra and its Treatment. With Report of 22 Cases.**—*Med. Times & Long Island Med. Jl.* 1931. Oct. Vol. 59. No. 10. pp. 362–363, 373–374. [12 refs.]

Twenty-two cases of pellagra admitted to the Philadelphia General Hospital are here reported. The author is of the opinion that the disease is on the increase owing to the privations consequent upon unemployment. Alcohol, too, is a causative factor in many cases. Reference to the literature shows that the disease is very rare among Jews. None of this nationality was found in the present series and it is claimed that "the well-known immunity of the Jewish people to pellagra has been built up by centuries of training in proper dietetics."

Treatment (successful in all cases except those with severe alimentary and nervous disturbances or other associated diseases) consisted of (1) Diet composed chiefly of milk, meat, green vegetables and eggs. (2) Brewers' yeast—2 teaspoonfuls in a cup of tomato juice, t.d.s. (3) Dilute hydrochloric acid, 10 minims t.d.s. *A. D. B.*

FRALIC (H. B.). **Pellagra; Report of Six Cases.**—*Med. Bull. Veterans' Administration.* 1932. Jan. Vol. 8. No. 1. pp. 56–60. [5 refs.]

Six cases of pellagra admitted to hospital in Minneapolis are described in detail. Apparently the disease is rare in this locality.

All the patients gave a history of deficient diet and those still living improved when given milk, eggs, fresh meat and vegetables together with yeast and arsenic. The author regards pellagra as an avitaminosis though in the State of Minnesota it has to be reported as a communicable disease. *A. D. B.*

MEYER (August). Sporadische Pellagra in Mitteleuropa. [**Sporadic Pellagra in Mid Europe.**]—*Klin. Woch.* 1932. Mar. 12. Vol. 11. No. 11. pp. 451–454. With 4 text figs. [7 refs.]

Three cases of pellagra at the University Clinic at Basle are described. All three cases were females, one having a long history of pyloric stenosis, and the other two being markedly alcoholic. The first case was relieved by radical cure of the gastric obstruction and one of the others by the exhibition of high protein diet, liver, yeast and hydrochloric acid. *A. D. B.*

WHEELER (G. A.). **The Pellagra-preventive Value of Canned Spinach, Canned Turnip Greens, Mature Onions, and Canned Green Beans.**—*Public Health Rep.* 1931. Nov. 6. Vol. 46. No. 45. pp. 2663–2668.

Canned turnip greens contain a satisfactory amount of pellagra-preventive vitamin and prove a practical and effective dietary supplement. Canned spinach is also useful in this respect but mature onions and canned green beans are poor sources of P-P factor. *A. D. B.*

LANGWORTHY (Orthello R.). **Lesions of the Central Nervous System Characteristic of Pellagra.**—*Brain.* 1931. Sept. Vol. 54. Pt. 3. pp. 291–302. With 7 figs. on 1 plate. [15 refs.]

Pellagra presents a variety of nervous system lesions affecting the brain, cord and peripheral ganglia everywhere. In most cases, however, one portion of the nervous system bears the brunt of the attack with consequent variations in clinical and pathological findings. A case described in detail in this paper may be summarized as follows :—

White woman, aged 22, presented typical skin, alimentary and neurological signs of pellagra. Apparently vomiting and diarrhoea had been present for 18 months. There was no definite history of diet insufficiency. At autopsy tuberculosis of the lungs and intestines was found and this may have accounted for faulty absorption of food from the alimentary tract. Histological changes in the nervous system were typical. These were very diffuse, involving all portions of the neurones. "Accumulations of pigment were found in cells of the sensory and autonomic ganglia and those in the spinal cord and brainstem. The antero-lateral columns of the cord were most severely involved; there was no abnormality in the posterior columns. The lesions involved particularly the spino-cerebellar and cortico-spinal tracts. It is probable that the neurological abnormalities were of only short duration; considerable fat could be demonstrated in the lateral columns of the cord. The small cells of the sensory ganglia showed the greatest deposit of pigment." The meninges of the cord and brain were somewhat thickened and there was an excess of Wilson's granules in the neurolemmal cells of nerve trunks. The heart was small and atrophied and the uterus was infantile.

A. D. B.

BALLIF (L.) & ORNSTEIN (I.). La cholestérolémie dans la pellagre aiguë. [**Cholesteraemia in Acute Pellagra.**]—*C. R. Soc. Biol* 1932. Jan. 29. Vol. 109. No. 3. p. 234.

Investigations of the blood cholesterol content in pellagra were made in 22 acute cases (4 women and 18 men). In 57 per cent. a hypocholesterolaemia was found and in only one case was the figure for cholesterol in excess of normal limits. There was no albuminuria and no evidence of either chloride or nitrogen retention in the urine. In 4 cases a slight increase in the blood urea figure was found but there was no association between this and the cholesterol content.

A. D. B.

TSCHERKES (Henriette). Chemische Blutbefunde bei Pellagra. [**Chemical Blood Examination in Pellagra.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1932. Feb. Vol. 36. No. 2. pp. 81–87. [18 refs.]

In July 1929 sixteen cases of pellagra were evacuated to Odessa from a district of the Ukraine where an epidemic of the disease (800

cases) had occurred. An opportunity was thus afforded of making certain routine chemical blood examinations. Previous to their evacuation the pellagrins had lived on an almost exclusively maize diet. On admission to hospital and during the two weeks in which the examinations were made the diet was mixed and sufficient, but still low in anti-pellagra factor.

Figures for blood sugar, non-protein nitrogen and potassium were found to be within normal limits, while the calcium content approached the highest level of normal fluctuations. There was also hypocholesterolaemia. *A. D. B.*

GUTHRIE (J. Birney). **Achlorhydria in Pellagra.**—*Jl. Trop. Med. & Hyg.* 1932. Mar. 1. Vol. 35. No. 5. pp. 71–74. [14 refs.]

During 1921–1925 the author made 35 gastric analyses in 93 pellagrins in the Charity Hospital, New Orleans. The findings obtained were compared with those published by other workers. A second series of 161 examinations out of 243 pellagra cases in the coloured female side of the same hospital is here recorded. Of these 161 analyses 13·04 per cent. showed excessive or normal gastric hydrochloric acid content, 18 per cent. showed deficiency and 68·9 per cent. complete absence of acid. In a series published by TURNER in 1930, achlorhydria was found in 85·2 per cent. of pellagrins.

Other points of interest are (1) Histamin injections increased the gastric hydrochloric acid content in 27·5 per cent., decreased it in 12·5 per cent. and caused no change in 52·5 per cent.; (2) There was an average occurrence of diarrhoea in 58·1 per cent. of the achlorhydria cases and in 41·8 per cent. of cases in which acid was present in the stomach. These figures provide an obvious therapeutic indication; (3) The occurrence of hydrochloric acid in a case of pellagra gives a somewhat better prognosis, though achlorhydria is no absolute criterion of severity. *A. D. B.*

SMITH (James H.). **The Influence of Solar Rays on Metabolism, with Special Reference to Sulphur and to Pellagra in Southern United States.**—*Arch. Intern. Med.* 1931. Nov. Vol. 48. No. 5. Pt. 2. pp. 907–1063. With 135 charts in text. [122 refs.]

The great length of this paper permits an abstract of the author's summary only.

Sulphur, in the form of the amino acid cystine, appears to protect low forms of life against solar radiation and the high concentration of this substance in the epidermal tissues of the higher animals is suggestive of a similar function. Cystine, in addition to its protective power against ultra-violet light, also promotes the growth of vitamin B and is connected with oxidative processes and with the detoxication of cyanogen compounds; all of which functions appear to be disturbed in pellagra. HOPKINS originally isolated glutathione (cystine combined with glutamic acid) from yeast, muscle and liver. Cystine is present in the anti-pellagra foods of GOLDBERGER and in amounts directly proportional to their preventive effect. There is some evidence, therefore, that lack of cystine may play a part in pellagra etiology.

Pigment is a protection against the superficial effects of solar rays. Now, pigmentation consists essentially in the deposit of melanin, a compound rich in sulphur. In this connexion it is interesting to note that the skin lesions of pellagra chiefly appear on exposed parts and

on parts which can phylogenetically be considered as such, e.g. the scrotum in man and the scrotum and tongue in dogs. That the effect of solar rays is not only superficial is suggested by the fact that pigmentation does not protect against pellagra as it does against sunburn; that pellagra shows a greater mortality in the white race; that "pellagra sine pellagra" is of doubtful existence in the view of many clinicians; and that sore tongue, diarrhoea and nervous changes are rare without associated dermatitis. It should also be remembered that an unhealthy organism is more susceptible to solar radiation than a normal one; thus "we may assume that normal tissue acts like a slow photographic plate and diseased tissue like a fast one."

Since the investigations of SULLIVAN and his co-workers (1919–1920) it has been recognized that sulphur metabolism in pellagra is faulty. Restoration of normal exogenous sulphur metabolism following an attack of the disease is not immediately accompanied by normal endogenous metabolism of this element. Excretion of thiocyanate in urine and saliva is decreased as also is that of urinary creatinine, though VOEGTLIN found in the urine an increase in neutral (unoxidized) sulphur. A loss of neutral sulphur in the cerebrum and spinal cord and an increase in the cerebellum have been recorded. Other workers have found that an adequate supply of cystine is necessary to maintain cyanide-detoxifying power in pellagra. Achlorhydria and absence of pepsin may adversely influence the splitting off of sulphur from the protein molecule.

To show the relative parts played by faulty diet and sunshine in pellagra three observations from the literature are quoted:—

"(1) Spontaneous pellagra and Goldberger's convicts, (2) spontaneous black tongue and Goldberger's dogs and (3) Enright's Germans and Bigland's Ottomans, prisoners of war in Egypt. In each of the three comparisons it would seem that when dietary deficiency is obvious and outstanding (the second instance in each group) in comparison with exposure to light, the effect partakes of a general or systemic reaction or type (. . . as opposed to a 'dermal' type in which the cutaneous lesions are relatively conspicuous), dermal effects readily attributable to direct exposure to light are at a minimum, scrotal lesions are relatively high, and mortality, when it can be compared, is great."

The age and sex incidence of pellagra run parallel to certain metabolic changes and there is a relationship between the geographical distribution of the disease and climate. In conclusion it may be stated that sulphur appears to protect the body against solar rays, that an inadequate supply of sulphur in the form of cystine plays an important part in pellagra causation, and that abnormal sulphur metabolism is a feature of the disease. A consideration of pellagra distribution and prevalence suggests that under certain abnormal conditions of nutrition solar rays may be an important factor in etiology. *A. D. B.*

WHEELER (G. A.). **A Note on the History of Pellagra in the United States.**—*Public Health Rep.* 1931. Sept. 18. Vol. 46. No. 38. pp. 2223–2229.

As early as 1864, GRAY of New York and TYLER of Massachusetts each reported a case of pellagra. These are probably the earliest cases on record in the U.S.A. This long-standing history of the disease is in accordance with the author's findings during his epidemiological studies of pellagra (begun in 1916) in Spartanburg and the

neighbouring counties of South Carolina. A questionary was sent to all doctors in the district who had been in practice prior to 1903 asking whether they had seen cases of pellagra previous to its general recognition in the Southern States (1907–1908). 62 replies were received and 38 reported having seen one or more cases prior to this time, the earliest being in 1885.

During 1917 a house-to-house canvass in this area revealed a total of 1,147 cases of pellagra out of a population of 22,653 (an incidence of 50·6 per thousand). It is estimated that only 10–15 per cent. of these came to the attention of a physician. The principal argument, therefore, against the existence of pellagra to any considerable extent in the South prior to 1907 loses much of its weight ; especially since the clinical descriptions of the disease at that time were very meagre and even misleading. The so-called diagnostic triad, diarrhoea, dermatitis and dementia, is now known to represent a severe or terminal picture of pellagra rather than essential symptoms of an ordinary case. Moreover, these symptoms must have been confused with other and, at the time, better known conditions, since following the recognition of pellagra the records of Southern States asylums show a compensatory decline in such other conditions

It is not contended that pellagra was very prevalent in the Southern States prior to 1907 but it is a question how much the magnitude of the epidemic in that and following years depended upon economic conditions and how much upon increased clinical knowledge and pellagraphobia. *A. D. B.*

ERULKAR (Abraham S.). A Case of Pellagra treated with Injections of Sodium Thiosulphate.—Reprinted from *Bombay Med. Jl.* 1932. Mar. 2 pp.

PANAYOTATOU (Angélique). Sur trois cas de pellagre. Une espèce de " Monilia " isolée des selles et du pharynx de ces trois cas.—*Rev. Méd. et Hyg. Trop.* 1932. Mar.–Apr. Vol. 24. No. 2. pp. 70–78. With 3 text figs.

RUTLEDGE (Winston U.) & KELLY (Robert). An Epithelioma secondary to Pellagrous Dermatitis.—*Arch. Dermat. & Syph.* 1931. June. Vol. 23. No. 6. pp. 1072–1075. With 2 text figs.

THATCHER (Harvey S.). Pellagra : Etiology (Modern Theories) and Pathologic Anatomy. [A Review.]—*Arch. Pathology.* 1931. Dec. Vol. 12. No. 6. pp. 970–982. [95 refs.]

VELARDE (A. Acosta). Pelagra.—*Bol. Asoc. Med. de Puerto Rico.* 1932. Apr. Vol. 24. No. 199. pp. 144–146.

SLEEPING SICKNESS.

SAUNDERS (G.). **Annual Report on Trypanosomiasis by the Pathologist at Yeji.**—*Gold Coast Rep. of Laboratory Services Year 1929–1930.* Appendix F. pp. 39–49.

During the year 34 cases of human trypanosomiasis were diagnosed. Of these 26 came for treatment, and the remainder were more or less unwilling victims caught during surveys of villages. Trypanosomes were found in all except one advanced case, who had previously had Bayer, and two advanced cases, who had increased cell counts in the cerebrospinal fluid. The methods of diagnosis were as follows :—

Examination of fresh blood	13
Gland juice	8
Centrifuged blood	2
Inoculation of blood into animals	7
Inoculation of C.S.F. into animals	1
Cell count C.S.F.	2
Clinical condition	1
	34

Great difficulty was found in demonstrating trypanosomes in some of the cases. If fresh blood examination was found to be negative once, subsequent examination never revealed trypanosomes unless there was a febrile relapse. In general the same applies to gland puncture. Efforts to establish strains in rats by inoculation of blood with abundant trypanosomes failed. It was found, however, that monkeys would take a human strain, and that dogs would take it if they were afterwards given an intraperitoneal injection of olive oil, as suggested by KLIGLER and WEITZMAN. Comparative direct inoculations showed that kittens or monkeys were better than dogs, and that dogs were better than rats. A number of details are given showing the use of olive oil injections for the isolation and maintenance of human strains in laboratory animals.

Details are given regarding the distribution of the disease in the Gold Coast. The report also contains a number of observations on treatment by an intensive course of atoxyl, and also some observations on the adhesion phenomenon, but these have been published elsewhere and noticed in this *Bulletin.* *W. Yorke.*

SAUNDERS (G.). **Annual Report on Trypanosomiasis by the Pathologist at Yeji.**—*Gold Coast Rep. of Laboratory Services Year 1930–31.* Appendix A. pp. 8–16. With 3 charts & 1 map.

During the year numbers of cases of clinical sleeping sickness, and of enlarged glands, came to Ejura for examination, but only a comparatively small proportion proved microscopically to be positive. The cases dealt with during the year are classified as follows :—

Remaining from last year	9
New infections	90
Total	99
Sleeping sickness not proved microscopically ...	74
Enlarged glands not proved to be trypanosomiasis ...	208

The routine treatment adopted was similar to that used by MACLEAN in Rhodesian sleeping sickness, viz., five injections of 1 gm. each of Bayer 205 in three weeks, followed, with or without a month's interval, by a course of tryparsamide. When mental symptoms were well-marked tryparsamide was given first. In general, it might be said that this line of treatment almost always cures, except in patients who were moribund or had other debilitating diseases, or had been starved. Details of the results obtained are given in tables.

A few fairly advanced cases were treated with a new preparation "Hoechst 4,002," but the results were not very encouraging. The areas from which they came are indicated in a map. This probably bears some relation to the actual incidence of the disease, but there are complicating economic and psychological factors which obscure it to some extent.

A number of observations were made on the adhesion phenomenon, from which the author reached the following conclusions :—

"1. A positive adhesion phenomenon gives a strong presumption that the subject has had trypanosomes in his body.

"2. No relationship has yet been noted between the strength of the adhesion test and either prognosis or history.

"3. A strain of trypanosomes may lose its power of reacting in the test."

W. Y.

SAUNDERS (G. F. T.) & MORRIS (K. R. S.). **The Distribution of Human Trypanosomiasis.**—*West African Med. Jl.* 1932. Jan. Vol. 5. No. 3. pp. 39–45. With 1 map & 4 figs. on 1 plate.

The following summary is given :—

"1. Investigation into the amount of human trypanosomiasis was carried out in Eastern Ashanti and the Eastern Gonja district of the Gold Coast. At first a few compulsory surveys of villages were made, but later cases came in voluntarily. This latter method was found to be vastly superior to compulsory surveys in that it maintains the friendship and co-operation of the people.

"2. Search for trypanosomes in suspected cases was made by examination of blood and gland juice, and if this failed, by centrifugalisation and animal inoculation. The number diagnosed by the first method formed only sixty per cent. of the total cases found.

"3. The area of operations falls naturally into two types of country :—the orchard bush savannah which prevails in the North, and is replaced in the neighbourhood of Ejura by the rain forest of Ashanti extending southward.

"4. In the savannah country *G. palpalis* and *G. tachinoides* are the predominant species of tsetse, and are confined strictly to the vicinity of rivers and streams.

"In the forest region *G. palpalis* and *G. longipalpis* occur, but with a far wider and more uniform distribution.

"5. In the savannah the majority of infection occurred along the line of the river, where there are most flies, and along the line of the main road, where there are most people, with a maximum of infection where these intersect.

"In the forest the distribution of cases showed no relation to either rivers or main roads.

"6. More infection was found in permanent than in temporary fishing villages on the Volta although the latter are far more heavily fly-infested. This can be explained by the annual evacuation of these camps breaking the vicious circle of man-fly-man infection.

" 7. Comparison of this with previous surveys of trypanosomiasis in the Gold Coast seems to indicate an increase ; but the method of approaching the people and the careful technique in diagnosis would account for the larger number of cases found.

" 8. The distribution of cases shown by the map looks like an introduction of the disease. However the correlation of the disease with concentrations of human and tsetse might equally well explain this distribution.

" 9. A formula is suggested for correlating man, fly and trypanosome. As a first approximation.

$$K\,t = f\,P \quad \text{.....(1)}$$

is given ; K being a constant, t is number of cases, P is the population, and f the fly density-activity.

" This should apply to small villages, but in large towns the fly-man contact depends roughly on the circumference of the town, and, for an average of v villages, the formula becomes

$$K\,t = f\sqrt{Pv} \quad \text{.....(2)}$$

" 10. Difficulties in applying the formula lie mainly in the estimation of f. There is some uncertainty as to which species of tsetse are significant carriers here.

" Within our experience sleeping sickness never occurs away from *G. palpalis* ; but *G. longipalpis* has been found infected with *T. gambiense* ; *G. tachinoides* is a proved carrier elsewhere ; and *G. morsitans* and *G. submorsitans* are possible carriers.

" *G. palpalis* shows a preference for human and domestic animal food and is inclined to concentrate round village water holes, ferries and fords, which gives it increased opportunity as a vector.

" A fairly close correlation has been found between the density of *G. palpalis* and rainfall in savannah country. From this a table is given for the estimation of f for this species in this type of country.

" 11. For the estimation of t the simple proportion of cases diagnosed by blood and gland-juice to the total number found, which is as 2 to 3, must be taken, as a more precise mathematical correlation could not be found.

" 12. Two further factors complicating the use of the formula are occupational incidence of the disease and immunity. Fifty-three per cent. of the Yeji cases were occupational. Such discrepancies would at once be shown up by the formula.

" 13. Sleeping sickness is well known to the natives. Both Hausa and Ashanti names refer to some obvious symptoms, which may indicate a recent introduction of the disease.

" The Gonja name however has no reference to symptoms.

" 14. Human trypanosomiasis may have contributed in maintaining the paucity of population in the Mid Volta region of the Gold Coast, although it is probable that the original depopulation of these areas was brought about by Ashanti raids." *W. Y.*

MORRIS (K. R. S.). **Trypanosomes of Game in the Gold Coast.**—*West African Med. Jl.* 1932. Apr. Vol. 5. No. 4. pp. 65–67.

During the work on tsetse control on the Eastern cattle route in the Northern Territories of the Gold Coast, the author took the occasion of studying the trypanosomal infection of game, and the effect of the proximity of the cattle route on this infection. The majority of the animals examined were shot in the Gambaga district. *G. submorsitans* was found in very small numbers in parts of this district, and none of the fly belts approached very close to the cattle route. *G. palpalis* and *G. tachinoides* were abundant along all the streams and rivers, and where these crossed the cattle route there was an intimate connexion between cattle, fly and game. The majority of these fly belts

were cleared by March, 1929, but at the heaviest fly belt, where game was particularly abundant, tsetse remained in the clearing in numbers up to September, 1929, the end of the rainy season. In the following dry season, and throughout 1930, there was practically complete exclusion of the fly from all the clearings.

The author considers separately the examinations of game made in 1929, when the cattle-fly-game connexion was only just broken, and examinations made in 1930, when there was a complete break in this connexion. The results of the examinations are given in a table.

The author summarizes his conclusions as follows :—

" The indications are that in this area *T. tragelaphi* is a normal parasite of game animals, probably tsetse-borne, and that the pathogenic trypanosomes occur in the game only when introduced by tsetse from cattle, and that failing this source of infection they will disappear.

"*Glossina tachinoides* is certainly a carrier of the latter trypanosomes, *G. palpalis* may also be involved, but *G. submorsitans* takes no part in transmission." *W. Y.*

UGANDA PROTECTORATE. **Annual Report of the Human Trypanosomiasis Research Institute for the Year ended 31st December, 1931** [DUKE (H. Lyndhurst), Director].—11 mimeographed pp. 1931. Entebbe.

Duke commences his report with stating that 1931 has been " a year of disappointment, confusion, and retrenchment." He describes in detail the financial misfortunes which have overtaken his laboratory and their results. The Institute in its modified form will in future dispose of a revenue of £4,500 per annum and will come under the control of the Uganda Government. The staff has been considerably reduced. Curtailment of the original program, especially on the side of biochemistry, will be necessary ; but the surviving unit is self-contained and well equipped, and it is confidently expected that it will be possible to carry out field work in addition to the maintenance of experiments at the laboratory. A summary is given of the work done during the year. This has already, for the most part, appeared in the form of publications which have already received notice in the *Bulletin*. *W. Y.*

PARIS EGUÍLAZ (Higinio). Contribución al estudio de la epidemiología de la enfermedad del sueño en los territorios españoles del Golfo de Guinea. Trabajo dedicado al Comité Internacional de Higiene de la Sociedad de Naciones. [**Epidemiology of Sleeping Sickness in the Spanish Possessions in the Gulf of Guinea.**]—167 pp. With 7 folding maps. French summary at the close of each chapter. 1932. Madrid. [6 pesetas.]

In his preface the author states that in 1927 he was appointed a member of the Colonial Sanitary Service of the Spanish Territory in the Gulf of Guinea. Disagreement with the conduct of the Sanitary Service on matters relating to the campaign against sleeping sickness resulted in his leaving the Service in December, 1928. He records that in April 1928, he had felt it to be his duty to inform the President and Director of the Colonies of his views on the result of the sanitary campaign against sleeping sickness. He stated that the results in

Fernando Po would be minimal and after a short time the consequences for Continental Spanish Guinea would be disastrous. The author continued to live in the Colony collecting information during the years 1929 to 1931 and events have more than justified his pessimism of 1928. The present work summarizes the observations he made during the three years in question.

Chapter I contains an historical account of sleeping sickness in Spanish Territory in the Gulf of Guinea. The existence of the disease was recognized in Fernando Po in 1908, but cases were apparently rare and, as the subjects were mainly agricultural labourers, it was considered that the disease was imported from the continent. A Commission appointed in 1909 recorded the presence of sleeping sickness both in the Island and on the mainland. In the author's opinion the internment of German subjects from the Cameroons during the War exerted a profound influence on the spread of the disease. This is not surprising as about 15,000 persons, almost all natives from infected regions in the Cameroons, were disembarked at Fernando Po. Numerous cases of sleeping sickness were found amongst the interned and almost all had been infected before reaching the Island. In 1909 there were two foci of infection in Fernando Po, one at San Carlos and the other at Concepcion, but in 1919 the disease had spread all over the Island. Similarly, for much the same reason, the disease had, during the period, spread greatly in the continental Colony.

Chapter 2 discusses the state of affairs in Fernando Po disclosed by the inquiry of 1927. There seems to be no doubt that by this time the disease had acquired a great intensity; in Santa Isabel and its environments from 8 to 17 per cent. of the people were infected, in the coastal region from Santa Isabel to Concepcion 14 to 20 per cent. and at Baho over 50 per cent. In the western coastal region from San Carlos to Basakato approximately the same proportion was infected. *Glossina palpalis* had by this time spread over the entire coastal region.

In the next chapter the author deals with the efforts of the Sanitary Service to combat the disease. The only method of diagnosis employed was the examination of thick blood films. This method had the great disadvantage of not disclosing more than 50 per cent. of the positive cases, and consequently a great number escaped unrecognized from Fernando Po to the Colony of Spanish Guinea and to the neighbouring colonies. Also the monthly published records were fallacious in that they underestimated the true number of infected persons. During the years 1927 to 1929 the sleeping sickness patients were treated in hospital and at times more than 600 patients were there under treatment. As the mortality greatly increased owing to the poor hygienic conditions of the hospital the procedure was eventually abandoned and replaced by ambulatory treatment. The patients came to hospital for their injections and then returned home; but this method had the objection that the people spread the infection in their peregrinations. In view of the small size of the island and the facilities of communication, the author considers the treatment should be given in the villages and in the plantations, thus avoiding so far as possible the movement of the infected.

In Chapter 4 an account is given of the present state of affairs in Fernando Po. Sleeping sickness now extends over the entire coastal region. The mortality, although stated in the report of 1927 to be

slightly diminishing, is in reality stationary. Glossina in abundance infests the entire coastal region.

Chapter 5 deals with the distribution of the disease in Spanish Guinea. The proportion of infected varies greatly according to whether the natives have worked in Fernando Po or have never left the continent, and even among the latter it is much greater in those who have worked in the coastal region. Up to 1925 only certain portions of the coast were infected, but during recent years the disease has gradually spread over the entire colony. During the years 1928 to 1931 the average morbidity has increased by more than 33 per cent. and in certain places it has now actually reached 100 per cent. The mortality rate has likewise become much more serious and in certain places has reached disquieting proportions. *Glossina palpalis* is distributed in more or less great numbers over the entire colony.

The rapid spread of sleeping sickness is the cause of an extremely difficult situation in Fernando Po, the interests of which are exclusively agricultural. The recruiting of agricultural labourers from Liberia has been absolutely suspended since the beginning of 1930, and the frontiers of the continental colony and those of the Cameroons and of Gabun are closely watched to prevent the passage of natives into the Spanish Territory and their recruitment for work in Fernando Po. Consequently, the only source of labour for the Island is Spanish Guinea. Moreover, the chiefs and the general native population are so unfavourably impressed by the fact that the great proportion of those returning from the Island are infected with sleeping sickness that they are offering more and more resistance to further recruitment. In fact it is now only possible to obtain labour by methods of recruitment concerning which the author prefers to say nothing.

The report closes with a lengthy chapter on the methods whereby the author considers the situation could be successfully combated.

W. Y.

NAJERA (Luis). La trypanosomiase humaine dans l'île de Fernando Póo. [**S.S. in Fernando Po.**]—*Medicina Países Cálidos.* Madrid. 1932. Jan. Vol. 5. No. 1. pp. 34–39.

The author draws attention to certain points which have been impressed upon him whilst responsible for 3,500 cases of sleeping sickness in the hospital at Fernando Po. On the question of diagnosis he believes that the simplest and most practical method is the examination of thick preparations of the peripheral blood. This method permits a diagnosis to be made in 70 per cent. of cases at the first examination, no matter what the clinical condition. The author, however, does not regard this percentage as sufficient. Gland puncture practised by skilled persons gives a higher proportion of successes, but this method was not found practicable in the hands of native assistants. In order to obviate the defects of the thick film method, examination was repeated 6 and 12 days later.

The author states that he has studied the cycle of the trypanosome in the peripheral blood during a period of four months, and that he has observed in untreated patients that the cycle is of two well-defined types. In the acute cases, the parasitic curve rises to a point where it remains for 5–15 days. This exacerbation is followed by a phase in which trypanosomes are not found ; the duration of this negative phase is almost equal to that of the preceding exacerbation. In

chronic cases, or better in old cases, the trypanosome is frequently present in the blood but in small numbers (2 or 3 per thick drop preparation). In treated patients on the other hand the cycle is much more complex and varied. The author concludes from this that there does not exist a certain means of parasitological diagnosis, and that in doubtful cases the best procedure is the examination of thick blood preparations repeated at several days' interval.

Another important matter is the determination of the period of disease. For this the examination of the cerebrospinal fluid is necessary, but in the author's opinion it is better to rely on the globulin reaction than on the enumeration of the cells, because the former procedure is easier and simpler. In the three following tables the results are given of the examination of 300 patients in different stages of the disease :—

I.—Relation between the clinical state and the globulin reactions.

Clinical state	Nonne-Apelt			Noguchi			Takata-Ara			Pandy		
	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%
Stage 1 ...	183	44	24·04	165	5	3·03	181	57	31·49	89	13	14·61
,, 2 ...	77	50	64·93	76	10	13·15	76	55	72·36	38	18	47·36
,, 3 ...	46	44	95·65	45	20	44·44	46	46	100·00	15	15	100·00
Total ...	306	138	45·09	286	35	12·23	303	158	52·14	142	46	32·39

II.—Relation between the quantity of albumen and the globulin reactions.

Albumen in gms. per litre.	Nonne-Apelt			Noguchi			Takata-Ara			Pandy		
	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%
0·19 or < ...	69	1	1·44	68	0	0·00	69	2	2·89	27	0	0·00
0·20 to 0·39	131	37	28·24	115	3	2·60	129	51	39·53	67	8	11·94
0·40 to 0·59	72	63	87·50	69	13	17·39	71	71	100·00	34	24	70·58
0·60 or > ...	34	33	97·05	34	19	55·88	34	34	100·00	14	14	100·00
Total ...	306	134	43·79	286	35	12·23	303	158	52·14	142	46	32·39

III.—Relation between the cells and the globulin reactions.

Num. of cells per cmm.	Nonne-Apelt			Noguchi			Takata-Ara			Pandy		
	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%	Num. cas.	Re-act. pos.	%
0–9 ...	182	26	14·28	165	1	0·60	179	39	21·78	86	5	5·81
10–49 ...	57	47	82·45	55	3	5·45	57	53	92·98	28	17	60·71
50–99 ...	19	18	94·73	19	5	26·31	19	18	94·73	9	6	66·66
Over 100 ...	48	47	97.91	47	26	55·31	48	48	100·00	19	18	94·73
Total ...	306	138	45.09	286	35	12·23	303	158	52·14	142	46	32·39

These three tables show the comparative value of the reactions of Nonne-Apelt, Noguchi, Takata-Ara, and Pandy. According to these figures the reaction of Takata-Ara, which is the easiest technique, gives the greatest percentage of positive results, but that of Pandy discloses the greatest specificity. The author believes that suboccipital puncture is preferable to lumbar puncture.

Referring to the treatment of the disease, great stress is laid on dietary. An inadequate diet will frequently change simple carriers of the trypanosomes into severe cases of sleeping sickness. It is not simply a question of food deficient in quantity or quality, but in a great number of cases the monotony of the diet. *W. Y.*

JAMOT (E.). La lutte contre la maladie du sommeil au Cameroun. [**Campaign against S.S. in Cameroon.**]—*Ann. Inst. Pasteur.* 1932. Apr. Vol. 48. No. 4. pp. 481–539. With 14 text figs.

This lengthy article should be consulted in the original by those interested. The author summarizes his conclusions as follows :—

The method of prophylaxis, which is in operation in the Cameroons, has for its primary objective the destruction of the reservoir of the virus in the circulation, thus controlling the foci of infection and preventing their extension. It is proposed in the second place to cure those patients who are curable. Diagnosis is made by examination of the blood and gland juice. The search for the infected is fundamental for the author's method of prophylaxis. All inhabitants without exception ought to be visited periodically. This cannot be left to subordinates and the doctor himself must direct the inspection.

All patients are treated energetically by such drugs as atoxyl, tryparsamide, novarsenobenzol, emetic of aniline, moranyl and orsanine. It does not appear to the author necessary to perform lumbar puncture before prescribing treatment. The trypanocidal action, that is to say the prophylactic action of the treatment, is controlled by blood examination.

All the contaminated areas have been examined and all patients discovered have been treated ; but efforts have been particularly concentrated on the great foci of central and eastern Cameroons. The limits of these foci have been carefully determined. All the patients discovered have been provided with a tally and registered, and they are revisited periodically and treated. As the result of this treatment, the indices of new morbidity and of the virus in the circulation, which are the criteria of the efficacy of the procedure, have been considerably reduced.

In the subdivision of Yaoundé, the new morbidity amongst the Mvelés fell from 36 and 52 per cent. in 1926–1927 to 0·9 and 1·3 per cent. in 1930, and amongst the Manguinass from 17·8 per cent. in 1928 to 0·04 per cent. in 1930. At Akonolinga, it fell from 42 per cent. in 1922–1923, and 23·2 per cent. in 1926–1927, to 2 per cent. in 1930. Amongst the Badjoués of Lomié it fell from 60 per cent. in 1926 to 19·9 per cent. in 1928 and 4·1 per cent. in 1930. At Bertoua and at Deng-Deng it decreased from 28·6 in 1928 to 0·2 per cent. in 1930. The indices of the virus are reduced proportionally, and consequently so is the risk of infection.

These figures show that in all the foci the scourge is on the retreat, but this does not mean that it is everywhere vanquished. Near places where the disease is rapidly disappearing there exist zones of

resistance and even occasional spots where it is taking the offensive. The conflict is consequently not over, but the gains are already considerable.

In many regions, but lately infected, the disease has become a rarity. The old cases are gradually disappearing. The mortality from sleeping sickness has decreased notably and its toll is often less than that of the general mortality of uninfected regions. The birth-rate increases in equal degree. In two words sleeping sickness in the Cameroons is no longer an important factor in the death rate, fall of the birth rate, and depopulation. *W. Y.*

CORSON (J. F.). **Experiments on the Transmission of** *Trypanosoma brucei* **and** *Trypanosoma rhodesiense* **to Man.**—*Ann. Trop. Med. & Parasit.* 1932. Mar. 19. Vol. 26. No. 1. pp. 109–115.

The author points out that one of the chief problems in the study of human trypanosomiasis is the relationship between the three polymorphic trypanosomes, *T. gambiense*, *T. rhodesiense* and *T. brucei*. In the production of numerous posterior-nuclear forms in the blood of experimental animals, and in its susceptibility to human serum, *T. brucei* resembles *T. rhodesiense*, and the two parasites are only distinguished by the fact that one infects man and the other is not known to be able to do so. Attempts to distinguish the two by serological tests have not hitherto met with much success.

From the point of view of practical tropical hygiene, three important questions need investigation. One is whether *T. gambiense* becomes changed in its distinguishing characters by repeated cyclical passages through such tsetse flies as *G. morsitans*, *G. pallidipes* and *G. swynnertoni*. The second is whether *T. brucei*, occurring in areas where human trypanosomiasis is unknown, can infect man. The third question is what changes may occur in *T. rhodesiense* by prolonged stay in the bodies of the lower animals. The two latter questions may be summarized by saying that we need to find out if *T. brucei* can become *T. rhodesiense* or *T. gambiense*, or if *T. rhodesiense* can become *T. brucei*. TAUTE's well-known experiments support the working hypothesis that there is a polymorphic trypanosome of animals, *T. brucei*, that cannot infect man, and another, *T. rhodesiense*, that infects man and lower animals also. One of the most promising lines of research would be to transmit *T. rhodesiense* by one of the species of game tsetse through a series of antilopes, and finally to see if it had lost its infectivity to man ; in other words, if it became *T. brucei*.

The experiments with *T. brucei* and *T. rhodesiense* described in detail in this paper were carried out at Tinde, Tanganyika Territory.

The author summarizes his conclusions as follows :—

" 1. A strain of *T. brucei* that had been maintained by direct inoculation in various animals for four and a half years was found to be easily transmissible by tsetse flies to guineapigs. Two European volunteers did not become infected after having been bitten by these infective flies.

" 2. A strain of *T. rhodesiense*, that had been maintained by direct inoculation in goats and sheep for nineteen months, was found to be easily transmissible by tsetse flies to guineapigs. A European volunteer, inoculated subcutaneously with the blood of one of the infected guineapigs, became infected, the incubation period being six or seven days. The infection was transmitted from the infected man to rats by inoculation of

blood. It may be said that a strain of *T. rhodesiense* had not become converted into *T. brucei* by a stay of nineteen months in the bodies of goats and sheep.

"3. It would seem that domestic animals need to be taken into account as possible means of spread of sleeping sickness.

"4. It is very desirable that work with antelopes should be undertaken in order to advance our knowledge of the subject of animal reservoirs of human trypanosomes." *W. Y.*

CORSON (J. F.). **The Results of Successive Bites of an Infected Tsetse Fly.**—*Jl. Trop. Med. & Hyg.* 1932. May 2. Vol. 35. No. 9. pp. 136–137.

After referring to two facts, viz. (1) that Glossina may remain infected with *T. gambiense* for prolonged periods and probably for the whole of its life, and (2) that, if not very hungry, it frequently inserts its proboscis several times before sucking blood, the author passes to a description of an experiment performed with a specimen of *G. morsitans* which was infected with a strain of *T. rhodesiense* that had been maintained in sheep and goats for 19 months. The infective fly, kept alone in a small wide-mouthed bottle, closed with cotton mosquito gauze, was put to bite white rats. Having bitten a number of rats in succession, the fly was then fed on a guineapig. On two days, Jan. 14th and 17th, the fly bit three rats in succession during a few minutes and then a guineapig. All the animals that were bitten became infected. Details of the experiment are given in a table.

The following is the summary :—

"It was found that successive bites of an infective tsetse fly caused infection in laboratory animals in every case. It therefore seems likely that in Nature tsetse flies may cause many more infections than would be represented by the number of times that they fed. Apart from the difficulty of the morphological similarity of *T. rhodesiense* and *T. brucei*, it is difficult to see how local infectivity rates of tsetse flies, obtained by dissection, could be of much value in *T. rhodesiense* areas, even if the incidence of infection of man were much higher than is actually observed. The behaviour of infective flies may be so variable in regard to biting and feeding that the number of cases of sleeping sickness may have little relationship to the number of infective flies." *W. Y.*

CORSON (J. F.). **A Note on the Susceptibility of Some Birds and Wild Animals to Infection with** *Trypanosoma rhodesiense*.—*Jl. Trop. Med. & Hyg.* 1932. Apr. 15. Vol. 35. No. 8. pp. 123–124.

In previous papers [this *Bulletin*, Vol. 28, p. 920 and Vol. 29, p. 300] the author has described attempts to infect native fowls, guineafowl, francolins and hyrax by inoculation with *T. rhodesiense*. He here records further similar experiments made at Tinde. Two species of francolins were used, a larger and a smaller. Of the former 7 of 17 inoculated became infected, but none of 5 of the smaller species; 81 guineafowl were inoculated and 7 became infected; 30 domestic pigeons with no successes, and 2 Muskovy ducks both of which became infected.

Of 12 native fowls inoculated, one became infected. Of 21 hyrax all became infected. A young fox developed a fatal infection, as also did a young jackal. Two porcupines were inoculated and one developed a transient infection. A cane-rat developed an acute infection. One young warthog was bitten by an infective *Glossina*

morsitans and 3 others were inoculated subcutaneously. Apparently, none of the 4 became infected. The article concludes with the following remarks :—

" Similar experiments with tsetse flies would be of some interest, though it is unlikely that the results would be qualitatively different from those of transmission by inoculation. The results in the case of francolins, guinea-fowl, hyrax and warthogs, suggest that it would be worth while to sub-inoculate rats from considerable numbers of these creatures living in an area badly infested with ' game ' tsetse flies." *W.Y.*

LEGER (Marcel) & SICÉ (A.). Considérations sur les modifications pathologiques tardives du liquide céphalo-rachidien dans la trypanosomiase humaine. [**Late Changes in the Cerebrospinal Fluid in S.S.**]—*Bull. Soc. Path. Exot.* 1932. Apr. 13. Vol. 25. No. 4. pp. 340–347. With 3 charts in text.

In a previous communication [*ante*, p. 283], the authors have drawn attention to the fact that meningeal lesions may develop early in the course of human trypanosomiasis ; they found definite changes in the spinal fluid within 6 or 7 months of the commencement of the disease.

In the present paper they describe certain cases in which the meningeal lesions develop slowly and are but little marked ; and they ask themselves whether this is due to the fact that the meningeal barrier remains good for a longer period than usual, or whether it is due to a chronic meningo-encephalitis.

They find from this new support for their thesis that the classical division of sleeping sickness into " first stage " and " second stage " cases is not justifiable [*loc. cit.* p. 281]. As in syphilis—where one should no longer speak of primary, secondary and tertiary stages—so in trypanosomiasis, the meningeal lesions may appear at any time, either early or late.

The difficulty of clearing up the point is largely due to the fact that the great majority of patients are Africans who do not come voluntarily to complain of their health, but are only discovered in the course of systematic inspections. Consequently, the matter can only be investigated in Europeans in whom the commencement of the disease is usually noticed ; one can thus fix the approximate date of infection and by lumbar puncture the meningeal changes can be recognized long before the appearance of meningeal symptoms.

A number of examples of cases with late development of nervous lesions is given in detail. *W. Y.*

DE MARQUEISSAC (H.). Note sur les modifications que peuvent subir le sang et le liquide céphalo-rachidien des malades atteints de trypanosomiase à virus *gambiense* lorsqu'ils sont laissés sans traitement. [**Changes in the Blood and Cerebrospinal Fluid in Untreated Gambiense Infection.**]—*Bull. Soc. Path. Exot.* 1932. Apr. 13. Vol. 25. No. 4. pp. 317–319.

The author refers to the well-known phenomenon that trypanosomes may disappear spontaneously from the blood of a patient in the absence of treatment. The parasites undergo degeneration before their disappearance. It was decided to re-examine this question and also to ascertain what happened to the spinal fluid in patients left without treatment.

Twenty cases were selected and kept in hospital under observation. Examinations were made of the gland juice, of fresh and stained preparations of the blood, of the urine, the pulse, the formol-gel reaction, and of the cerebrospinal fluid. Three, and sometimes four, examinations of the blood were made daily at the same hours. No drug was given during the period of observation which varied from 11 to 51 days.

The 20 cases were classified as follows :—

5 patients with cerebrospinal fluid normal or but slightly changed.
3 patients with cerebrospinal fluid showing pronounced lymphocytic reaction, but without trypanosomes.
12 patients with very pronounced lymphocytosis, with an excess of albumose and with trypanosomes in the spinal fluid.

Sixteen of these 20 patients have had their cerebrospinal fluid re-examined after a period without treatment varying from 10 to 51 days. Of 5 in whom the cerebrospinal fluid at the beginning was but slightly altered, 3 showed an increase of lymphocytes, 2 an increase of albumose and 1 showed trypanosomes 16 days after the first puncture. The author asks himself whether it is necessary to blame the lumbar puncture ? Of 3 patients belonging to the second category the spinal fluid showed itself at each examination to be more rich in lymphocytes, but the amount of albumose was not changed.

Among the patients belonging to the third group, who had at the first examination parasites in the spinal fluid, important variations in the number of lymphocytes were observed ; but in none of the 12 cases did the trypanosomes disappear spontaneously from the spinal fluid.

There was no evidence that variations in the blood infection depended on the integrity of the nervous system, because the positive blood examinations in the three groups were respectively 65 per cent., 76 per cent. and 71 per cent.

In conclusion it is remarked that the formol-gel reaction was much more marked when the defensive powers of the patient were well developed ; in cachectic patients it might be negative. *W. Y.*

TOULLEC & ALAIN. Sur un cas de trypanosomiase africaine. [**A Case of S.S.**]—*Marseille-Méd.* 1932. Jan. 25. Vol. 69. No. 3. pp. 117–119.

Details are given regarding a Senegalese case of sleeping sickness infected in Haute-Volta. The man was admitted to hospital on the 26th November, 1931, repatriated from Tunis, with a diagnosis of emaciation, general poor condition, and bronchitis. The dossier of the case shows that he was enlisted for 5 years in January, 1923, and was sent to France and then Morocco. He returned to France in November, 1926, and from November, 1927, to February, 1928, he was given leave and went home. In July, 1929, he embarked for Bizerta, and since then he has lived in Tunis. The man had apparently remained in good health and without medical history until September, 1931. According to the author one of the chief points of interest regarding the patient is the length of the incubation period. The date of infection could not have been later than July, 1927 [?1929], and for more than two years afterwards the patient served in the army in a normal manner. Another point of interest was the large number of parasites in the peripheral blood, certain preparations of the blood containing one or two trypanosomes to a field. Notwithstanding intense mental symptoms, the cerebrospinal fluid was normal. It is probable, therefore, that these symptoms, which were of recent development, are to be attributed to the intensity of the infection. *W. Y.*

CHESTERMAN (Clement C.). **Some Results of Tryparsamide and Combined Treatment of Gambian Sleeping Sickness.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. May 14. Vol. 25. No. 6. pp. 415–435.

The observations recorded in this paper are the result of 11 years' work. They relate to 17 " first stage " cases and 251 " second stage " cases. The author presents his results in a series of tables. The first table gives details of the 17 " first stage " cases treated with various doses of tryparsamide. All these cases have been observed for periods varying from 4 to 10 years (mostly 7 to 10) since the termination of treatment, and all were cured. Tables II to V give the results obtained with patients who had been unsuccessfully treated with other drugs, e.g. atoxyl, tartar emetic, and stibenyl. In Tables VIa, VIb and VIc we find records of 140 cases treated by tryparsamide alone. The cases are grouped according to the size of the dose of tryparsamide administered. In the remaining tables the results obtained by combination of tryparsamide and other drugs are given.

The author summarizes his conclusions as follows :—

" *Treatment by Tryparsamide alone.*

" Later experience has necessitated a modification of the opinions expressed in previous publications by the author (1923, 1924 and 1925), when less drastic treatment was advocated and more prolonged courses deemed necessary [this *Bulletin,* Vol. 20, p. 694; Vol. 22, p. 139; Vol. 23, p. 58.]

" *First Stage* cases should receive six to eight weekly injections of medium doses (0·07 gram per kilo for children, 0·055 gram per kilo for young persons and 0·045 gram per kilo for adults). A second course is not necessary.

" *Second Stage* cases should receive six to eight weekly injections of large doses (0·09 gram per kilo for children, 0·07 for young persons and 0·06 for adults).

" The maximum dose for adult is 4 grams. It is permissible to use a preliminary medium dose, but definite grading is bad.

" *Advanced Second Stage* should receive two or three large doses at five-day intervals, then a rest for ten to fourteen days in order to appreciate the condition of the eyes. It is better to give a rest than to diminish subsequent dosage.

" The first four injections are probably the all important ones. Long continued treatment after resistance is established is useless as a hope of cure. So also are subsequent courses although life may be prolonged for many years. Such treatment may produce great tolerance with no visual trouble and patients are apt to become fat, flabby, and lethargic.

" *Results after Five Years* can be counted as accurate and it should be possible to cure at least 50 per cent. of second stage cases, and approximately 100 per cent. of first stage cases.

" *The Relapse.*—So-called relapses are in reality non-cures, owing to tryparsamide resistance. The appearance of trypanosomes in the blood, a phenomenon known to be very variable in untreated cases, is but an indication of their re-emergence from so-called inaccessible regions and little importance should be attached to their fortuitous discovery in the blood. It is not necessary to suppose the subsequent evolution of a resistant strain in old standing cases, the trypanosomes have probably been resistant from the first month of treatment and remained so. That the blood may remain free after repeated examination in non-cured cases may but be due to the fact that the multiplication of trypanosomes is retarded or actually prevented by the action of the drug on their metabolism.

" *The Cerebrospinal Fluid.*—To know the cell content of the C.S.F. at the commencement of treatment is of importance, more perhaps for the first stage case than for the second, for if it is normal the former need not be subjected to serious risk of optic atrophy.

"The response of second stage cases to the drug cannot be foreseen from the cell content of the C.S.F. nor do they react proportionally to it. The cell count can always be reduced to normal or very slightly raised figures by a course of tryparsamide but it is not possible to say that the patient is really cured. Time alone can tell that, a negative blood later on does not mean a cure necessarily, and a positive formol-gel serum does not mean a failure.

"A raised cell content a few weeks after the course need not indicate failure, for it may slowly progress to normal limits after the cessation of treatment. Resistant cases kept under the influence of tryparsamide, although going down hill may preserve a count of under 100 cells per mm., although the albumin content combined is disproportionally increased.

"*Combined Treatments.*—The association of tryparsamide and tartar emetic has not in our hands given better results than treatment by the former alone.

"The most promising combination is a course of tryparsamide as outlined above, preceded by two or three large doses of Bayer 205 (say three doses of 1·5 gram for an adult at three- or four-day intervals).

"A rest should then be allowed for ten to fourteen days or till the urine becomes practically free of albumin before administering tryparsamide in medium to large doses. Special care must be exercised if it is desired to preserve full vision at all costs.

"*Treatment in the Field.*—Proved first stage cases only should be left to the care of natives at bush centres where they should be treated by normal six to eight injections of medium doses of tryparsamide. If reasons of economy dictate, atoxyl or soamin may be substituted; or Bayer 205 may be used.

"Second stage cases (after diagnosis by lumbar puncture) should be given one to three doses of Bayer 205 as circumstances permit, pending their concentration at treatment centres supervised by a medical man.

"After the completion of the preliminary course of Bayer 205 he should then treat these patients (who must receive a liberal and accustomed diet) for other debilitating diseases such as the presence of helminths, taking care not to damage the liver by carbon tetrachloride, and then proceed to the course of tryparsamide carefully examining by simple tests the peripheral vision of *every* patient before *every* injection.

"We have no evidence of our own, nor have we seen any published records which would tend to modify the opinion expressed earlier by the author (1924) that Bayer 205 alone will not cure second stage cases.

"Second courses of tryparsamide are not justifiable either on grounds of economy, hope of cure or the prevention of contamination of glossina. If non-cured patients cannot be removed from fly areas they should receive blood sterilising injections of Bayer 205 every few months until death."

[This excellent and important paper is followed by a critical discussion, in which the reviewer, HANSCHELL, LOW and MURGATROYD took part.] *W. Y.*

MANSON-BAHR (Philip). **The Results of Treatment of African Trypanosomiasis in Europeans with Tryparsamide and Bayer 205.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1932. May 14. Vol. 25. No. 6. pp. 479–486. With 2 charts in text.

Since the publication in 1923 by Low and himself of cases of sleeping sickness treated by Bayer 205, the author has had an opportunity of observing 11 other cases of trypanosomiasis in Europeans over a considerable period. Three of these were *T. rhodesiense* infections, and the remainder were due to *T. gambiense*. Some of the cases, which relapsed clinically and parasitologically after intensive Bayer 205

treatment, were cured by subsequent tryparsamide, and *vice versa*. Clinical details of the 11 cases are given. Manson-Bahr states that his results appear to agree with those of CHESTERMAN in one important respect, viz., that combined treatment of trypanosomiasis is more effective than the pushing of one drug to the extremes of tolerance after parasitic relapses have occurred. Manson-Bahr considers that success does not depend so much upon the size of the dose or the length of the course of treatment, at any rate in first stage cases, but rather upon the age of the infection and the spacing of the drug. *T. rhodesiense* infections were the more difficult to cure. One case was treated immediately on the appearance of symptoms and showed no reaction to tryparsamide, but responded immediately to Bayer 205. Another case appeared at first to be equally resistant to both remedies but eventually recovered after suffering from serious disturbance of the vision ; it is doubtful whether this patient would have been cured unless the second course of tryparsamide had been pushed to the limit, because Bayer 205 had little effect.

The author thinks that Bayer 205 followed by tryparsamide gives the most hopeful outlook ; the former drug should be given to the extent of 3 gm. in the first week, and the subsequent tryparsamide injections should be given in tolerated doses. Three of the patients received as much as 6 gm. per week, but possibly this dose is too much for the average European. There was only one instance of optic neuritis and in this the damage was not serious, but it appeared as if tryparsamide dosage 10 months previously had rendered the patient more liable to toxic disturbance from this drug. *W. Y.*

SAUNDERS (G.). **The Results of the "Six Strong Injections" Course of Atoxyl.**—*West African Med. Jl.* 1932. Apr. Vol. 5. No. 4. pp. 64–65.

The results are given of the treatment of 26 cases of sleeping sickness by a course of "6 strong injections of atoxyl," i.e. 6 doses, each consisting of 2 cgm. per kilo., at intervals of 10 days. The maximum individual doses should not exceed 1·1 gm. Of the 26 cases 15 (58 per cent.) were apparently cured. The author points out that in estimating the value of this course it must be remembered that it was designed by the French for use in a very heavily infected country with an average infection rate of 29 per cent., reaching 77 per cent. in some areas. In such a country it is obviously justifiable to expose the individual to risks which would not be justifiable in less heavily infected areas. No such heavily infected areas have so far been found in the Gold Coast. The author is of opinion that the margin of safety between a curative dose and a blinding dose of atoxyl is so small that close supervision of its administration is necessary, and therefore the cheapness of atoxyl would be neutralized by the expensive organization necessary for its administration. *W. Y.*

DE MARQUEISSAC. Contribution à l'étude de l'emploi du 270 Fourneau (orsanine) dans le traitement de la trypanosomiase humaine. [**Orsanine in the Treatment of S.S.**]—*Bull. Soc. Path. Exot.* 1932. Mar. 9. Vol. 25. No. 3. pp. 252–260.

The author has tested the therapeutic value of 270 Fourneau or orsanine (o-oxy-p-acetylamino-phenyl arsinic acid) on a large number

of cases of trypanosomiasis in the first and second stages of the disease. Of 106 first stage cases, of which 97 had received no previous treatment, 87·5 per cent. were cured. In all, 251 second stage patients were treated, 213 of whom had had no previous treatment. The results were as follows :—Blood relapses 35 per cent. ; progressive evolution 13·1 per cent. ; prolonged amelioration 51·3 per cent. ; deaths 14·3 per cent. The doses given varied from 15 mgm. to 30–35 mgm. per kilo. and the total amount from 300 to 350 mgm. per kilo. of weight. The duration of treatment was 10 to 12 weeks.

The effect of the drug on the following points was investigated :—

1. *Weight of the patient.*—In 72 per cent. of cases the weight increased as the result of treatment.

2. *Effect on the lymphatic glands.*—The immediate result was a disappearance of the glands in 77·8 per cent. of cases, but after 2½ months this had fallen to 62·7 per cent. Every puncturable gland was negative whether the puncture was made immediately after treatment or two months later.

3. *Effect on blood sterilization.*—Immediate sterilization was observed in 96·7 per cent. of cases, and of 122 patients kept under observation for 2 months 95 per cent. remained sterile.

4. *Effect on the cerebrospinal fluid.*—In 28 cases the cerebrospinal fluid was examined before and after treatment ; the results are shown in the following table :—

Spinal fluid normal before treatment. 15 cases.		Spinal fluid abnormal before treatment. 13 cases.			
Normal after treatment.	Abnormal after treatment.	Not followed.	Normal after treatment.	Improved after treatment.	Stationary.
14	1	1	9	3	0

5. *Effect on the general condition.*—The observations made on 128 patients are summarized in the following table :—

	Before treatment.	Immediately after treatment.	Two months after the last injection.
	Per cent.	Per cent.	Per cent.
Bon état	28	70	78
Assez bon état	58	21	17
État général médiocre ...	12	8	4

A number of old cases of sleeping sickness which had previously been treated with other drugs (atoxyl or tryparsamide) were given orsanine. All these patients had parasites in their blood at the time orsanine treatment was commenced. The immediate result was peripheral sterilization in 19 (79 per cent.) of the 24 cases ; in 5 the blood remained positive. Before treatment the proportion of cases in bad condition was 37 per cent. After treatment it fell to 20 per cent. In 79 per cent. the weight increased, in 8 per cent. it remained stationary and in 13 per cent. there was a loss of weight.

Among the accidents following administration of orsanine vomiting was noted 17 times out of 151 cases and diarrhoea 12 times. The latter, which was, as a rule, only met with in bad cases, was sometimes very severe and caused cessation of treatment. Only one abscess resulted from 1,051 injections. Ocular troubles—both slight and grave—were occasionally observed. *W. Y.*

MURAZ (G.) & VAISSEAU (G.). De divers types d'arséno-résistance dans les traitements actuels (A.E.F.) de la trypanosomiase humaine. [**Different Types of Arsenic Resistance in Treatment of S.S.**]—*Bull. Soc. Path. Exot.* 1932. Mar. 9. Vol. 25. No. 3. pp. 260–279.

The author calls attention to the frequence of arsenic-resistance after the use of tryparsamide or trypoxyl (atoxyl), and the desirability in such cases of having recourse to mixed treatment. He also emphazises the necessity of prolonged observation, extending over years, of cases apparently cured. In addition he records a number of observations showing that feeble atoxylization may at times suffice to produce definite cure. The observations are grouped as follows :—

A.—Two cases of arsenic resistance showing that tryparsamide at times, after producing a transient amelioration, results in a pathological condition refractory to further treatment.

The authors believe that this condition is probably due to some change in the behaviour of the trypanosome. They suggest that it may have been produced by unsuccessful treatment with arsenicals of previous patients, from whom the infection was subsequently passed on to the two cases now described.

B.—Twenty-two cases of arsenic-resistance of trypanosomes of the peripheral circulation in relation to tryparsamide. This arsenical exerts a selective action on trypanosomes localized in the meninges, but often fails to sterilize the blood and lymphatic system.

In the present cases it was found that the treatment with tryparsamide had produced marked improvement in the cerebrospinal fluid, but that trypanosomes were still present in the blood. Therefore, after the treatment of second stage cases, it is necessary to examine the blood as well as the cerebrospinal fluid ; and also it is advisable to give two or three doses of atoxyl (10 mgm. per kilo.) before commencing with the tryparsamide.

C.—Six cases of arsenic-resistance to atoxyl showing different types of relapse after massive treatment with this drug.

Relapses, as shown by the blood, usually occur about 5 to 6 months after the end of treatment.

D.—Seven cases showing the possibility of a very gradual evolution of trypanosomiasis several years after courses of atoxyl which had been systematically repeated. This evolution was revealed by lumbar puncture, which showed a slight or marked change in the cerebrospinal fluid.

Consequently, it is necessary to follow the patients during many years.

E.—Thirteen cases in which atoxyl given alone, and often in comparatively feeble doses, had sufficed to produce complete sterilization. This complete sterilization is evidenced by a normal cerebro-spinal fluid, and by negative examinations of the peripheral blood 8 to 10 years after the original treatment.

During the course of the discussion on this paper, FOURNEAU stated that in his laboratory BOVET had observed that the various arsenical compounds exhibit different tendencies to produce arsenic-fast strains of trypanosomes. Usually, several passages are required and this is the case with tryparsamide and with orsanine. In exceptional cases, such as with oxymethylaminoarsinic acid, a single dose is sufficient and the strain so produced is resistant not only to this compound, but also to orsanine. FOURNEAU considers that this aspect of chemotherapeutic agents is of great importance. *W. Y.*

VAN HOOF (L.). Essai de deux nouveaux antimoniaux, le Dn 7 et le Dn 9, dans la trypanosomiase humaine. [**Trial of Two New Antimonials in S.S.**]—*Ann. Soc. Belge de Méd. Trop.* 1932. June 30. Vol. 12. No. 2. pp. 181–198.

The author tested the therapeutic action of two compounds received from the Union Chimique Belge on a number of cases of human trypanosomiasis. These substances, Dn 7 and Dn 9, had been previously tried on experimentally infected laboratory animals by DUBOIS [*ante*, p. 297]. Dn 7 is an antimonyl-bisoxyquinolin sulphurate of diethylamine and contains 16·7 per cent. of antimony. Dn 9 is the oxyquinolin stibio-sulphurate of diethylamine; it contains 34·38 per cent. of antimony in the pentavalent form.

Dn 7 was tried on 12 cases of sleeping sickness; it was well tolerated in doses of 0·25 to 0·50 gm. and was given intravenously. The first injection may produce transient symptoms, but they disappear during the course of treatment. There is no evidence of cumulative action or of intoxication. Peripheral sterilization is produced within an hour by a dose of 5 to 7 mgm. per kilo.: the duration of sterilization was about 15 days. The author believes that a dose of 0·5 gm. is well tolerated by the average native, but adds that it may be wise to give a preliminary dose of 0·25 gm. The drug can be given daily, but in practice it was given every other day, i.e. about 1·5 gm. per week. The exhaustion of his supplies prevented the completion of his observations.

Dn 9 was tried on 13 cases of sleeping sickness. It was well tolerated in the same doses as Dn 7 and seemed to produce less disturbance. Its action, however, was much less regular. The optimum dose was 0·5 gm. and it can be given every other day up to a total of 5 gm. without producing any trouble. Details of the cases treated by the drugs are given in two tables.

In a footnote it is stated that Dn 7 was given to an animal infected with an arsenic-resistant *T. gambiense*. The parasite was not destroyed by 0·08 gm. of atoxyl per kilo. A monkey of 1,810 gm. was cured by an intravenous injection of 0·02 gm. of Dn 7. *W. Y.*

VAN DEN BRANDEN (F.). Essai de traitement de la trypanosomiase humaine par une méthode biologique. [(**Unsuccessful**) **Treatment of S.S. by a Biological Method.**]—*Ann. Soc. Belge de Méd. Trop.* 1931. Dec. 31. Vol. 11. No. 4. pp. 395–397.

The author has tested on 9 cases of sleeping sickness the biological method of treatment advocated by ARNAUD. This consists in obtaining, aseptically, serum from a case of sleeping sickness in good condition, with trypanosomes in the blood, and storing it in the

incubator at 37°C. for 20 days. To 60 cc. of the serum, 40 cc. of the following mixture are added :—

Formol	0·5 cc.
Phosphoric acid	0·5 cc.
Physiological saline	39·0 cc.

The mixture is allowed to stand for 8 days and then is ready for use. The treatment consists in 4 injections at 3-day intervals, each consisting of 2 cc. of the above mixture and 8 cc. of venous blood.

None of van den Branden's 9 cases received the slightest benefit from the treatment. *W. Y.*

LAUNOY (L.), NICOLLE (P.) & PRIEUR (M.). De l'action synergique du 205 Bayer–309 Fourneau et de quelques composés organiques d'antimoine, dans la trypanosomiase expérimentale à *Trypanosoma congolense* de la souris. [**Synergic Action of Bayer 205 and Organic Compounds of Antimony in** *T. congolense* **Infection of Mice.**]—*Bull. Soc. Path. Exot.* 1932. Jan. 13. Vol. 25. No. 1. pp. 65–77. [23 refs.]

This work is a continuation of that previously described [this *Bulletin*, Vol. 27, p. 834 and Vol. 28, p. 906]. The authors found that "Fourneau 309" in doses of 4 mgm. to 5 mgm. per 20 gm. of mouse rarely cured mice infected with *T. congolense*. Similarly the trivalent antimonial compounds did not cause sterilization if given in doses not greater than 50 per cent. of the lethal dose ; and the pentavalent aromatic antimonial stibenyl caused only temporary disappearance of parasites if given in doses of at least 4 mgm. When, however, "Fourneau 309" and the antimonial compounds are given together, in the doses mentioned above, cures are not rare. The results, which are given in tables, show that sometimes as many as 80 per cent. of the animals are definitely sterilized. This is a typical instance of synergic action in therapy. *W. Y.*

MARZINOWSKY (E. J.). Ueber die kombinierte Wirkung von Novarsolan und ultravioletten Strahlen auf Trypanosomen. [**Combined Action of Novarsolan and Ultraviolet Rays on Trypanosomes.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1932. Vol. 74. No. 3/4. pp. 379–383.

Reference is made to the work of ROSKIN on the combined action of drugs and ultraviolet rays [this *Bulletin*, Vol. 28, p. 911–12]. The technique adopted by the author was similar to Roskin's. Twenty-five mice were infected simultaneously, and equally, with *T. equiperdum*, the hair on the back having been previously removed. On the 4th day, when trypanosomes were numerous in the peripheral blood, each mouse was given 1 cc. of a 1-3,000 solution of novarsolan per 20 gm. of weight ; 15 of the mice were then subjected to the action of ultraviolet radiation, and the remaining 10 were kept as controls. The results are set forth in a table, from which it is seen that the 10 control mice all died of trypanosomes within 6 to 14 days. Of the mice subjected to radiation, 2 died shortly after treatment, viz. on the 6th and 8th day respectively ; the remainder lived for 30 days or longer. None of them showed parasites in the blood. The author's results, therefore, are in complete accord with those of ROSKIN. *W. Y.*

RICHET (Ch.) Jr. & DUBLINEAU (J.). Pyrétothérapie associée ou non à l'arsénothérapie dans la trypanosomiase expérimentale de la souris (nagana). **Pyretotherapy in Nagana of Mice.** *C. R. Soc. Biol.* 1932. Mar. 4. Vol. 109. No. 8. pp. 641–643.

The authors have investigated the question whether heat, alone or associated with arsenical treatment, has any therapeutic action on mice infected with nagana.

The animals were warmed by being placed in an oven heated to 37° C. or even higher. This was not always well tolerated, and if the process was prolonged the mice died from heat stroke. As a rule, they tolerated heating to 37°C–45°C. for 2 hours daily. The results of numerous experiments showed that pyrexial therapy alone had no action on the infection. When, however, pyrexial therapy was associated with subcurative doses of N.A.B., it was found to have a definitely beneficial result, and sometimes even resulted in cure.

W. Y.

BROWNING (C. H.), COHEN (J. B.), COOPER (K. E.) & GULBRANSEN (R.). **The Trypanocidal Action of Some Derivatives of Anil and Styryl Quinolines. II.**—*Proc. Roy. Soc.* Ser. B. 1932. May. 2. Vol. 110. No. B768. pp. 372–377.

The therapeutic action of certain derivatives of anil and styryl quinolines on mice infected with *T. brucei* is summarized in a table. The styryl compounds described had a curative value. The papers are of a technical nature and should be studied in the original by those interested.

W. Y.

KOLMER (John A.) with the assistance of Anna M. RULE. **The Degree of Infection in Relation to the Parasiticidal Activity of Chemotherapeutic Compounds.**—*Jl. Pharm. & Experim. Therap.* 1931. Nov. Vol. 43. No. 3. pp. 521–529.

The author states that in conducting tests for the parasiticidal activity of chemical agents, the time of their administration in relation to the degree of infection may definitely influence the results. He gives the following summary of his experimental work:—

"1. Arsphenamin and neoarsphenamin were more effective when given to rabbits three to four weeks after intratesticular inoculation with *Spirochaeta pallida* and when orchitis had developed, than when given immediately after inoculation.

"2. Arsphenamin, neoarsphenamin, atoxyl, treparsol and other trypanocidal agents were more effective when given to rats eighteen to twenty-four hours after intraperitoneal inoculation with *Tr. equiperdum* than when given immediately or within twelve hours after inoculation.

"3. In other words these spirocheticidal and trypanocidal agents were more effective in the presence of early light infections than when given for abortive treatment immediately after inoculation.

"4. When administered after the infections had been given a longer start with a numerically heavier infection, the minimal curative doses were also larger.

"5. It would appear that the same principle applies to experimental streptococcus infections, that is, that smaller amounts of chemical agents are effective when given after the infection has become established than required if administered immediately after inoculation.

"For these reasons it is recommended that experimental infections be allowed to become established before chemical agents are administered for eliciting possible therapeutic effectiveness in chemotherapeutic investigations." *W. Y.*

i. REINER (L.) & LEONARD (C. S.). **Rôle of the NH_2, OH and As=As Groups in Parasitotoxic Action of Arsphenamine Derivatives.**—*Proc. Soc. Experim. Biol. & Med.* 1932. May. Vol. 29. No. 8. pp. 946–950.

ii. ——— & ———. **Toxic Action of Hydrogen Peroxide on Trypanosomes and a Note on Chemotherapeutic Mechanism.**—*Ibid.* pp. 951–953.

i. This paper is devoted to a consideration of some derivatives of arsphenamine mainly from a chemical point of view. As the results of experiments in which *T. equiperdum* was exposed to the action of various chemicals *in vitro* for 15 to 60 minutes apparently at room temperature, the authors come to the following conclusion :—

"1. Hiramatsu's reaction" [(colorimetric reaction) between neoarsphenamine and osmic acid] "is given by compounds possessing aminophenol groups and the presence of arsenic is not necessary. 2. p-Aminophenol is not toxic to trypanosomes, but its autooxidation product, probably iminoquinone, is highly toxic. Reducing agents, such as sulfite, thiosulphate and thiol compounds, inhibit the toxic action. 3. Quinone is toxic to trypanosomes and its toxicity is inhibited by thioglycollate. 4. Various organic arsenious oxides, not capable of giving on oxidation iminoquinone structure, are more toxic to trypanosomes than are oxidized aminophenol and quinone. 5. The toxicity of arsphenamine derivatives to trypanosomes is due chiefly to the presence of trivalent arsenic and not chiefly to hydroxyaminophenyl groupings, although these may contribute to the *in vitro* toxicity."

ii. In this paper similar experiments were performed by exposing *T. equiperdum* to the action of hydrogen peroxide ; this is followed by a discussion of the possible part played by the production of peroxides (during the biological oxidations) in relation to the action of arsenicals. The authors come to the following conclusion :—

"Hydrogen peroxide is toxic to trypanosomes. The formation of traces of H_2O_2 under conditions where the catalase content of the system is low cannot be excluded. Such concentrations, although not detectable, might be sufficient to exert some damaging action on trypanosomes. While this factor is probably negligible *in vivo*, it still might be involved with the rate of the —AsO formation and thus concerned indirectly with the chemotherapeutic activity of arsenicals (Santesson)." *W. Y.*

VON JANCSÓ (N.). Mechanismus der Arzneifestigkeit bei Protozoen. Zur Frage der Parasitotropie chemotherapeutischer Mittel. [**The Mechanism of Drug Resistance in Protozoa.**]—*Zent. f. Bakt.* I. Abt. Orig. 1932. Mar. 30. Vol. 124. No. 3/4. pp. 167–176.

The author has previously shown [*ante* p 291] that trypanosomes exposed *in vivo* to trypaflavin become photo-sensitive, presumably owing to the drug they have absorbed. Trypaflavin-fast strains and arsenic-fast strains do not become photo-sensitive in this way. In the present paper he shows that trypanosomes exposed to compounds of the styrylquinoline series (BROWNING, COHEN, ELLINGWORTH, GULBRANSEN) become photo-sensitive in the same manner. If mice infected with normal trypanosomes are injected intravenously with

pyronin, the trypanosomes in the blood become stained within a few minutes, and this is likewise the case in mice injected with styrylquinoline. But if mice infected with trypaflavin-fast, or with arsenic-fast, strains are treated with these two drugs, the trypanosomes do not become stained.

Rats weighing 180 gm. infected with the normal strain were injected with 4 mgm. trypaflavin subcutaneously, and one hour later they were killed. The trypanosomes in the blood were centrifuged off and the trypaflavin extracted from them with absolute alcohol. From 0·4 cc. of the deposit of trypanosomes (dry weight 18 mgm.) there was extracted 0·24 mgm. trypaflavin. He concludes that one-eighth of the drug which had been injected had been taken up by the trypanosomes. The same experiment was performed with rats infected with arsenic-fast and with trypaflavin-fast strains, but from the deposit of trypanosomes only a trace (0·009 mgm.) of trypaflavin could be extracted. Similar experiments were performed in mice and also in rats treated with styrylquinoline. He concludes from these experiments that resistant trypanosomes have lost the power to absorb active drugs, a power possessed by normal trypanosomes. This is in harmony with EHRLICH's conception of drug-resistance.

The following summary is given by the author :—

By the use of a new method, it has been possible to demonstrate, and analyse quantitatively, the action which occurs between the chemotherapeutic agent and the parasite in the body of the host. By means of the author's photo-biological method, drugs which have a photo-dynamic action can be demonstrated quantitatively in individual trypanosomes. Strongly coloured drugs, pyronin, 2(p-acetylaminostyryl)-6-dimethylaminoquinolin-methosulphate, *i.e.*, styrylquinoline) produced vital staining of the trypanosomes and can be seen within the flagellates. Especial importance is attached to the demonstration that it is easily possible by isolation of the trypanosomes from the treated animal, and extraction of the same with suitable solvents, to regain quantities of the drug which can be colorimetrically estimated. By these experiments, there can be demonstrated the decisive importance of parasitotropism for the production of a curative action.

Investigations with drugs of the acridin-, pyronin-, and styrylquinoline-series in animals infected with *T. brucei* have shown that normal trypanosomes absorb these compounds in the body of the host to an astonishingly large extent, while drug-resistant trypanosomes take up these drugs in comparatively small amounts. This is a demonstration of the correctness of Ehrlich's conceptions, for a difference of the powers of absorption could determine the curative effect only if the chemotherapeutic agent exerts its action directly. The point of attack of the drug lies within the parasites.

Considerable light is thrown upon the nature, mechanism and importance of drug-resistance by the investigations here published.

[This work confirms the results reached by the reviewer and his colleagues *vide* this *Bulletin*, Vol. 28, p. 910.] *W. Y.*

VON JANCSÓ (N.). Beobachtungen chemotherapeutischer Vorgänge im Fluorescenzmikroskop. [**Observations on Chemotherapeutic Processes by the Fluorescence Microscope.**]—*Klin. Woch.* 1932. Apr. 16. Vol. 11. No. 16. p. 689.

This is a short paper continuing the account of the author's experiments with trypanosomes exposed to trypaflavin [*ante*, p. 291–2]. In the present paper he worked with a fluorescence microscope illuminated

with ultraviolet light invisible to the unaided eye. Under such circumstances, trypanosomes and red blood corpuscles are normally invisible. Infected mice were injected with various drugs, such as trypaflavin, pyronin, and styrylquinoline, and the blood containing trypanosomes examined under the fluorescence microscope. Under these circumstances, they were found to have become clearly visible owing to the fluorescence of the drugs which they had absorbed. It was also possible to observe the distribution of the drug in the trypanosome, since in the trypanosomes exposed to styrylquinoline the nucleus was especially conspicuous and, to a lesser extent, the blepharoplast. After trypaflavin the blepharoplast was conspicuous.

When arsenic-resistant trypanosomes were exposed to these drugs in this manner and then examined, they remained invisible, showing that they had not absorbed any of these drugs. This confirms the author's previous experiments on this subject. *W. Y.*

NEUMANN (Harry). Die chemotherapeutische Abheilung der Trypanosomeninfektion bei jungen Tieren. [**The Chemotherapeutic Cure of Trypanosome Infections in Young Animals.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1932. Vol. 74. No. 1/2. pp. 177–181.

Details are given of experiments in which it is shown that in rats infected with trypanosomes (Nagana Prowazek), and subsequently treated with antimosan or myosalvarsan, relapses are more common, and occur earlier, among the young animals than among the adults. The author believes that this is due to defective immune body formation in the young animals. *W. Y.*

KROÓ (H.). Antigenwert und chemotherapeutischer Heilerfolg. Ein Beitrag zum Wesen der chronischen Infektionen. [**Antigen Value and Chemotherapeutic Effect.**]—*Klin. Woch.* 1932. Feb. 20. Vol. 11. No. 8. pp. 316–317.

In a previous publication (1931) the author has shown that a strain of *Spirochaeta pallida*, which has been made experimentally resistant to immune serum, has lost the capacity of producing spirochaeticidal antibodies. In the present work he has extended his observations into the realm of trypanosomal infections.

He states that it is a recognized fact that different strains of trypanosomes of the same species may exhibit differences in their susceptibility to arsenicals. He collected three strains of nagana, e.g. "Prowazek," "Hamburg," and "Ferox"; mice infected with the first were always cured by 0·5 cc. of a $\frac{1}{4000}$ solution of neosalvarsan, whereas those infected with the other strains usually relapsed.

In the first group of experiments 8 mice were infected with each of the strains and 24 hours later were given a dose of neosalvarsan, which was certainly curative, i.e. 0·5 cc. of a $\frac{1}{200}$ solution. Seven days later each mouse was given a similar injection of the homologous strain; only 1 of the "Prowazek" mice became infected, but practically all of the "Hamburg" and "Ferox" mice. From these experiments it is concluded that the more susceptible "Prowazek" strain produced better immunization than did the other two strains which were less susceptible to the action of arsenicals.

In the next experiments rabbits were injected intravenously with similar doses of the three strains, and 10 minutes later given a sterilizing dose of neosalvarsan (0·05 gm. per kilo.). Seven days later they were bled and the trypanocidal power of their inactivated sera, against each of the three strains, tested by incubation of the parasites *in vitro* for 1 hour in different dilutions of the immune serum, and subsequent injection of the mixture into normal mice. The mice injected with the treated "Prowazek" strain did not become infected, whereas the others did. From this it is concluded that the chemotherapeutic influence and the antigen value of a parasite are in some way correlated. Somewhat similar experiments conducted with original and relapse strains gave very much the same results. *W. Y.*

SCHILLING (Claus) & NEUMANN (Harry). Zur Methodik der immunologischen Differenzierungsmethoden von Trypanosomenstämmen. [**The Theory of the Method of the Immunological Differentiation of Trypanosome Strains.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1932. Apr. Vol. 36. No. 4. pp. 214–229. With 1 text fig.

Biological methods play an important part in the differentiation of trypanosome species; thus *T. brucei* is killed by human serum, whereas *T. gambiense* is not. For the differentiation of different strains of one species, or of the relapse trypanosomes of one strain, we are absolutely dependent upon immuno-biological reactions. The most important methods for the differentiation of such variants are (1) Preliminary treatment with dead parasites and re-infection, (2) Cure and then re-infection, and (3) Serum experiments (*in vivo* and *in vitro*).

In the course of numerous experiments, the authors found it necessary to ascertain which of these methods was most useful, and how far the reaction can be considered to be specific. They pass to a critical examination of each of the three methods.

1. *Preliminary treatment with dead antigen and re-infection.*—After referring briefly to other work on this method, the authors describe their own technique. They reached the general conclusion that the method is not suitable for the differentiation of trypanosomes, mainly because no adequate protection is afforded the mice by the preliminary injection of dead trypanosomes.

2. *Drug cure and re-infection.*—The only drugs found to produce certain cure of infections due to the authors' old laboratory strains were salvarsan and "Bayer 205." An experiment is described in which three series of mice infected respectively with three different strains of *T. brucei*, viz. "Prowazek," "Ferox" and "Nagana 30," were cured with an intravenous injection of 0·5 cc. of a 1 : 500 solution of neosalvarsan. Each of the mice was re-infected 8 days later with its homologous strain. The results, which are set forth in a table, show that the mice infected with strain Prowazek were immune to re-infection, whereas the others were not. It is therefore concluded that strain Prowazek furnishes the best antigen.

3. *Serum experiments.*—The serum used in these experiments was obtained from animals in which the infection ran a chronic course; in all 103 sera were used; they were obtained from 2 cases of human trypanosomiasis, and from horses, sheep, goats, a calf, a dog, rabbits,

guineapigs and mice. The freshly obtained centrifuged serum was heated at 45°C. for 30 minutes, whereby all remaining trypanosomes were killed. The serum was then stored in the ice-chest for 1–20 days (as a rule 1–3 days) until it was required for an experiment. To 0·5 cc. of the serum 0·1 cc. of a weak trypanosome suspension was added, and, after an hour's sojourn in the incubator, the mixture was injected into mice. By means of this technique it is possible to distinguish between the original Prowazek strain and the original "Ferox" or "Nagana 30" strains. That is, "Prowazek" immune serum protected against the Prowazek strain, but not against "Ferox" or "Nagana 30" and *vice versa*. Similarly the technique allowed of the differentiation of the original and relapse strains. A large number of experiments are described and must be consulted in the original by those interested. The authors conclude that the serum experiments constitute far the best immunological method for trypanosome differentiation. *W. Y.*

SCHNITZER (R.). Untersuchungen zur Chemozeptorentheorie. VIII. Mitteilung. Das Tantalsystem. Die biologische Struktur des "Arsenozeptors." [**Investigations on the Chemoreceptor Theory. VIII. The Tantalum System. Biological Structure of the "Arsenoreceptors."**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1932. Vol. 75. No. 1/2. pp. 143–155. With 1 text fig.

In this paper the author resumes his experiments on the phenomenon of "Chemotherapeutic Interference." As an example of a drug which produces "interference" he used potassium hexatantalate, the action of which was described by MORGENROTH and ROSENTHAL in 1911. He finds that the tantalate will interfere with the chemotherapeutic action of tartar emetic, of salvarsan, and of arsenophenylglycine, but not with that of trypaflavine, arsacetin, or aminoxyphenylarsenoxide. On the other hand, parafuchsin "interferes" with the action of the arsenoxide, but not with that of arsenophenylglycine. From this and previous experiments he elaborates a somewhat complicated theory of the structure of the chemoreceptor-mechanism; for the details of this theory the original paper should be consulted. In its broad outlines, the theory postulates that the chemoreceptor consists of two parts: firstly, a primary binding nucleus (Bindungskern), which is non-specific and which combines with the chemotherapeutic agent, and secondly, "toxo-sensitive groups" (giftempfindlichen Gruppe) highly specific for each particular drug. During the production of drug-resistant parasites it is these latter toxo-sensitive groups which undergo a change. He explains "Chemotherapeutic Interference" on the supposition that parafuchsin combines with the primary binding-nucleus, and so prevents the taking up of more toxic drugs, such as trypaflavine; and he compares the action of parafuchsin in this respect to that of Ehrlich's "toxoids." He considers that there are two main binding-nuclei, *viz.*, that reacting with parafuchsin and that reacting with tantalate. The first combines with trypaflavine, pentavalent arsenicals, and arsenoxides; and the second with tartar emetic and arsenophenylglycine. Salvarsan combines with both, but more strongly with that corresponding to parafuchsin. *W. Y.*

NATTAN-LARRIER (L.) & NOYER (B.). Ultrafiltration et pouvoir protecteur des immun-sérums anti-trypanosomes. [**The Protective Power of Filtered Immune Sera.**]—*C. R. Soc. Biol.* 1932. Mar. 11. Vol. 109. No. 9. pp. 702–704.

It has been shown in previous papers [this *Bulletin*, Vol. 28, p. 371 and Vol. 29, 303] that the protective and curative substances of human serum traverse collodion membranes which will hold back alexine. In the present work the authors have subjected to ultrafitration the sera of animals infected with trypanosomes and have inquired whether the filtered serum possesses the same protective power as the unfiltered serum. It was found that collodion membranes which allow the passage of the protective and curative substances in human serum arrest the corresponding substances of immune serum. The same membranes under similar conditions likewise arrest alexine, the natural anti-sheep haemolysin of human serum, the anti-syphilitic sensibilisatrice, and the anti-sheep haemolysin obtained in the rabbit.

W. Y.

NATTAN-LARRIER (L.), NOYER (B.) & BÉDIER (E.). Action de la chaleur sur le pouvoir anti-trypanosome du sérum humain. [**Action of Heat on the Anti-Trypanosomal Power of Human Serum.**]—*C. R. Soc. Biol.* 1932. June 3. Vol. 110. No. 19. pp. 241–244.

As the result of their filtration experiments [*ante*, p. 303] the authors consider that it is necessary to distinguish between the curative substance and the protective substance of human serum. In the present work they have inquired whether the two substances behave differently when exposed to the action of heat. A number of experiments are described in detail from which it is concluded that exposure to a temperature of 59°C. for a sufficient period enfeebles the curative power and destroys the protective power of human serum. Consequently, the authors believe that the protein molecules of the protective substance are larger and less resistant to heat than are those of the curative substance. *W. Y.*

SCHEFF (Georg). Ueber den intermediären Stoffwechsel der mit Trypanosomen infizierten Meerschweinchen. [**Intermediate Metabolism of Guineapigs infected with Trypanosomes.**]—*Biochem. Ztschr.* 1932. May 14. Vol. 248. No. 1-3. pp. 168–180. [10 refs.]

In this paper the author continues his observations on the metabolism of experimental animals infected with *T. equiperdum*, using guineapigs instead of rats [this *Bulletin*, Vol. 27, p. 242]. From his results he comes to the conclusion that the biochemical processes which cure infected guineapigs are essentially the same as those which cure infected mice, with this difference, that certain peculiarities can be observed, corresponding to the longer duration of the disease and the undulating course of the infection, which are not seen in rats. The fundamental changes found are the following:—

1. A hypoglycaemia, which reaches its most extreme degree shortly before the death of the animal, but which can also be seen during the earlier stages, although to a less extent, every time the trypanosome count reaches a high degree.

2. A hyperglycaemia is observed a few days after the diminution of trypanosomes. This is especially marked following the cure produced by germanin at an advanced stage of the infection; but it can also be seen in a less marked degree during the spontaneous diminution in the number of trypanosomes during the earlier periods.

3. A hyperlipaemia in the advanced stages of the infection.

4. Considerable diminution of the glycogen and diminution of the neutral fat in the liver even in the later stages of the infection. The author interprets these changes roughly as follows:—

When trypanosomes are numerous in the blood they tend to utilize large amounts of glucose, so producing the hypoglycaemia, and this tendency to hypoglycaemia is increased by the damage suffered by the liver (as shown by blood-sugar curves after diminution of glucose). To counteract this the body of the host increases its output of glucose; and when the number of trypanosomes rapidly diminishes (following the administration of germanin or as a result of spontaneous crisis) this increased output of glucose results in hyperglycaemia for several days. The increased fat content of the liver results from the damage which it has suffered, and it is complementary to the diminished glycogen content. The author considers that these metabolic changes are not specific for trypanosomiasis, but occur also in other infections.

Observations are also recorded on changes in the serum proteins of infected animals. Seven tables are given in which the biochemical changes observed are clearly recorded. *W. Y.*

THOMSON (J. G.) & DE MURO (P.). **The Influence of *Treponema duttoni* on an Infection with *Trypanosoma rhodesiense* in Mice.** —*Jl. Trop. Med. & Hyg.* 1932. Feb. 1. Vol. 35. No. 3. pp. 33–36. [10 refs.]

After a brief reference to observations indicating that one infection may be antagonistic to another, the authors pass to a description of their own work on the influence of *Treponema duttoni* on *T. rhodesiense* infections in mice. The effect of these two organisms on one another could be determined with accuracy owing to the constant and uniform results produced by each separately on mice. *Treponema duttoni* usually appeared in the peripheral blood of mice about the 4th day after inoculation; they became numerous on the 5th and 6th days, but on the 7th, 8th and 9th days they were either entirely absent from the blood, or present in only very small numbers. They reappeared on the 10th, 11th and 12th days, thus producing the first relapse, disappearing again on the 13th and 14th days, reappearing once more on the 15th, 16th and 17th days, thus reproducing the second relapse, and disappearing finally about the 28th day. In mice inoculated with *T. rhodesiense* the trypanosomes appeared in the blood about the 3rd day and increased in number until the death of the mouse on the 5th, 6th or 7th days.

The effect of the spirochaete infection on that of the trypanosomes was tested at various stages of the disease, but the most striking results were obtained when spirochaetes and trypanosomes were inoculated simultaneously. Marked effects were also produced when trypanosomes were inoculated on the 8th day or immediately after the first spirochaetal crisis. Details of the experiments are shown in tables. The lives of 21 mice were markedly prolonged when spirochaetes and trypanosomes were inoculated simultaneously. Spirochaetes and

trypanosomes disappeared from the blood simultaneously, from which the authors conclude that some trypanocidal substance develops in the serum simultaneously with the disappearance and destruction of the spirochaetes. After the mice have recovered from the relapsing fever infection they quickly succumb to trypanosomiasis. *W. Y.*

DE BRAUWERE (P.) & LISFRANC (J.). Un essai de prophylaxie anti-trypanosomique au " Bayer 205 " et au " Tryponarsyl Meurice." [**Prevention of S.S. by Bayer 205 and Tryponarsyl.**]—*Ann. Soc. Belge de Méd. Trop.* 1931. Dec. 31. Vol. 11. No. 4. pp. 387–393.

With the object of ascertaining the prophylactic value of Bayer 205 and of " tryponarsyl Meurice," the authors have undertaken experiments among the people of the Semlik plain. Trypanosomiasis has ravished the population of this district during the last twenty years, and in the particular part where the authors' experiment was undertaken, the disease, which had been sporadic for some time, became definitely endemic in 1926. The following table shows its progress since that time :—

Year.	No. examined.	New cases.	Percentage.
1926	?	14	?
1927	1,319	41	3·1
1928	1,317	69	5·2
1929	2,009	297	14·78
Feb. 1930	3,058	376	12·30

The experiment was undertaken during the months of March and April, 1930. The first group received three weekly injections of 1 gm. of Bayer 205, and the second 5 injections of 2 gm. of tryponarsyl Meurice at fortnightly intervals. All suspected cases were carefully eliminated.

1. *Bayer 205 group.*—This experiment was carried out at Capita Makora, 38·7 per cent. of the population of which were infected. Seventy-six adults were given 3 doses of 1 gm. of the drug, 23 adults 2 doses of 1 gm., 17 children 3 doses of 0·5 gm., and 7 individuals 3 doses of 0·2 gm. The results of the experiments are summarized in the following table :—

Date.	No. examined.		Found to be infected.	
	Injected.	Controls.	Injected.	Controls.
2. 6. 30	105	7	–	–
20. 9. 30	106	32	1	7
17. 2. 31	95	14	8	4
19. 6. 31	87	31	6	–

2. *Tryponarsyl Meurice group.*—This experiment was undertaken in four heavily infected villages, about a quarter of the population of which was infected. The first injections were given on the 4th March, 1930 : 224 adults received 4 doses of 2 gm. of the drug, 114

adults 3 doses of 2 gm., 35 adults 2 doses of 2 gm., 93 children 4 doses of 1 gm., 31 children 3 doses of 1 gm., and 12 children 2 doses of 1 gm. The injections were complete on the 23rd April. The results are summarized in the following table :—

Date.	No. examined.		Injected found to be infected.						Controls found to be infected.
			Gland infections.			Lumbar puncture.			
	Injected.	Controls.	4 inj.	3 inj.	2 inj.	4 inj.	3 inj.	2 inj.	
31. 5. 30	414	530	–	–	–	–	–	–	16
25. 9. 30	385	1,719	–	–	–	–	–	1	76
21. 2. 31	356	2,182	7	4	2	–	1	–	62
15. 6. 31	335	1,512	1	2	2	2	–	1	49
			8	6	4	2	1	2	203
			23						

The author concludes from this work that in order to cause the disappearance of a focus of the infection by prophylactic medication, it would be necessary to repeat the procedure every six months. The choice of the drug will probably be Bayer 205 because of the convenience and rapidity of its administration, and the possible danger of producing resistance by insufficient doses of tryponarsyl.

W. Y.

DE MARQUEISSAC (H.). Contribution à l'emploi du Moranyl (205 Bayer, 309 Fourneau) donné à titre préventif dans la trypanosomiase humaine (secteur de Pagouda, Togo). [**Preventive Use of Moranyl in S.S.**]—*Bull. Soc. Path. Exot.* 1932. Apr. 13. Vol. 25. No. 4. pp. 347–353.

The author has carried out an experiment in three villages of Lama-Tessi designed with the object of ascertaining the value of Bayer 205 given prophylactically. The population is very dense ; at the recent census in 1931, the number of inhabitants was found to be 19,690 in an area of 240 sq. kilometres. The percentage found to be infected with trypanosomes was 18 in 1927, 35 in 1928, 40 in 1929, 3·2 in 1930, and 5 per cent. in 1931.

The three villages chosen for the experiment were Assire with 9 per cent. of new cases at the 1931 census, Kagnessi with 7 per cent. of new cases, and Siou-kaoua with 3 per cent. of new cases. Each inhabitant selected for the experiment was the subject of two examinations of the blood and one of the gland juice ; the dates of these examinations were 25th July, 1931, for Assire, 6th August for Kagnessi, and 29th August for Siou-kaoua.

The individuals who were negative and who were clinically quite healthy were divided into two lots ; pregnant women and very young children were excluded. The first group were given Bayer 205 and the second kept as controls. Each individual moranylized (Bayer 205) had his counterpart from the point of view of age, weight, and family in the control group. So far as possible one brother was moranylized

and the other not, and one sister was placed in each group, as also were husband and wife. By this means it was endeavoured to make the experiment as fair as possible. Each moranylized individual was given one injection of 0·02 gm. of Bayer 205 per kilo. of weight.

All the cases, treated and untreated, were re-examined between 20th and 30th November, 1931, i.e. 123 days after treatment in the case of Assire, 109 days in the case of Kagnessi, and 82 days in the case of Siou-kaoua. The results are given in the following table :–

Villages.	Age and sex.	No. moranylized.	No. of controls.	Period between injection and examination in days.	No. of moranylized and found positive.	No. of controls found positive.	Index among moranylized. %	Index among controls. %
Assire ...	Men ...	33	32		5	1	15	3
	Women ...	21	21	123	2	1	9	4·7
	Children ...	41	42		4	4	9·7	9
	Total ...	95	95		11	6	11·5	6·3
Kagnessi ...	Men ...	19	21		2	2	10	9·5
	Women ...	15	15	109	2	2	13	13
	Children ...	24	29		5	4	20	13
	Total ...	58	65		9	8	15	12
Siou-Kaoua ...	Men ...	30	28		3	2	10	7
	Women ...	20	22	82	2	1	10	4·5
	Children ...	47	47		1	4	2	8·5
	Total ...	97	97		6	7	6	7
Conclusions	Men ...	82	81		10	5	12	6
	Women ...	56	58		6	4	10	17
	Children ...	112	118		10	12	8	10
	Total ...	250	257		26	21	10	7
	General total ...	507			47		8·5%	

After stating that these figures are disappointing, the author passes to a consideration of previous observations on the prophylactic value of "Bayer 205" in human trypanosomiasis and in experimental trypanosomiasis of animals. Finally, he lays down certain conditions which he considers should govern any future experiments of this kind.

W. Y.

CLARK (Herbert C.) & DUNN (Lawrence H.). **Experimental Studies on Chagas' Disease in Panama.**—*Amer. Jl. Trop. Med.* 1932. Jan. Vol. 12. No. 1. pp. 49–77.

The recent discovery of Chagas' disease in Panama has aroused considerable local interest, since the clinical and pathological records of the Panama canal zone have shown no entry of a case of this disease during the past twenty-seven years. The authors' studies have consisted in searching for *T. cruzi* in blood smears of large numbers of children and of numerous animals, of inoculations with the parasites

into other animal hosts, and of the collection of a large number of *Triatoma geniculata*, the arthropod believed to be the principal invertebrate host of the disease in Panama, with observations on the infections of these insects with trypanosomes.

The first case of human trypanosomiasis found in Panama was that of an infant admitted to Santo Tomas Hospital on the 1st December, 1930. This case and two others discovered about three months later have already been reported by MILLER [this *Bulletin*, Vol. 28, p. 922]. The 4th infected child was discovered on March 2nd 1931, and a 5th on August 20th 1931. The authors give the following summary of their work :—

" 1. Five cases of Chagas' disease have been found in children in Panama during the past ten months.

" 2. Rabbits, guineapigs and white rats were inoculated and became positive with heavy infections from one of these human cases. This strain was successfully transferred to a monkey, guineapigs, white rats, white mice and bats.

" 3. A young dog naturally infected with trypanosomes that appear to be identical with those found in the human cases was discovered at the home of the first human case.

" 4. Guineapigs, white rats and white mice were infected through inoculation of blood from a naturally infected dog. This strain was carried on to other guineapigs and a bat.

" 5. Twenty-eight armadillos, *Dasypus novemcinctus fenestratus* Peters were examined and six, or 21·4 per cent., were found to be infected with a trypanosome that we believe to be *T. cruzi*.

" 6. Eighty-one opossums, *Didelphis marsupialis etensis* Allen, were examined and twenty or 24·6 per cent. were found infected with what was apparently *T. cruzi*.

" 7. A squirrel, kept as a pet in the house where two cases of Chagas' disease lived proved to be infected with a trypanosome identical with *T. cruzi*. This was the second occasion in which a pet, in the same household with one of the five human cases, was found positive for trypanosomes.

" 8. Bats infected with a trypanosome believed to be *T. cruzi* were found in Panama. A total of 161 of these flying mammals was examined and 30, or 18·6 per cent. proved to be infected. Those found positive represented 5 species.

" 9. The trypanosome of the bats was readily transmitted to dogs, guineapigs, white rats and white mice.

" 10. Ninety specimens of *Triatoma geniculata* were collected in the Chilibrillo Caves. This completes a record of infected Triatoma, infected bats and an infected opossum found in the same chamber of these caves.

" 11. The feces of 55·5 per cent. of the bugs proved to contain trypanosomes.

" 12. Twenty-six guineapigs were each inoculated with a macerated *Triatoma* and 21, or 80·8 per cent., became positive.

" 13. Seven guineapigs became infected through *Triatoma geniculata* feeding upon them. It was not determined whether these infections were caused through the bites of the bugs or through infection with their feces.

" 14. The incubation period of the experimentally infected animals varied from three to twenty-eight days.

" 15. The degree of the infection in the experimentally infected animals varied considerably. One guineapig had a peak peripheral infection of more than 1,600 trypanosomes in a thick blood film.

" 16. The persistence of infectivity has extended in 1 guineapig for more than two hundred and seventy-eight days.

" 17. Although all our laboratory animals could be infected with this trypanosome the guineapig seemed to be the most satisfactory for experimental purposes. The adult animals proved so susceptible to infection that no very young ones were used.

" 18. The trypanosomes soon disappear from the peripheral blood of the human cases. Infected animals have lived for a considerable number of days since the beginning of their infection and in some of them trypanosomes have been found for many days.

" 19. Leishmania forms of the trypanosome have been found in the hearts of some animals but others fail to show them.

" 20. Our experience indicates that this trypanosome does not possess a high degree of virulence. However, we cannot read what the future holds in store in the way of remote serious sequelae." *W. Y.*

DIAS (Emmanuel). Le *Trypanosoma cruzi* pendant les premières phases de l'infection expérimentale. [*T. cruzi* **in the Early Stages of Experimental Infection.**]—*C. R. Soc. Biol.* 1932. May 27. Vol. 110. No. 18. pp. 203–205.

After experimental inoculation of small animals with *T. cruzi*, the parasites appear in the peripheral blood within a few hours and remain almost constant in number during the first four days. On the 5th day there is a sudden increase in number due to invasion of the blood by parasites which have multiplied in the tissues.

The intracellular evolution in the tissues is similar to that in the bug and *in vitro*. The crithidial forms have but a very short existence and are quickly transformed into young forms (thin and very motile flagellates). During the first acute phases of the infection the intracellular cycle is completed within 5 days.

The initial distribution of the parasites varies according to the site of inoculation. After subcutaneous inoculation, some of the parasites pass into the blood, whilst others penetrate the cells of the neighbourhood and multiply there intensely; some of those which pass into the blood remain there and some become localized in various organs. After peritoneal inoculation the parasites gradually escape into the blood or tissues. Phagocytosis is quite exceptional.

The author observes that he has not seen the initial blood phase after inoculation of the intestinal contents of infected Triatoma into guineapigs and mice; the trypanosomes in these cases are not found in the blood before the 11th day. *W. Y.*

DIAS (Emmanuel). Le *Trypanosoma cruzi* et ses rapports avec le système réticulo-endothélial. [**The Reticulo-endothelial System and** *T. cruzi* **Infection.**]—*C. R. Soc. Biol.* 1932. May 27. Vol. 110. No. 18. pp. 206–210. With 3 text figs.

As mentioned in the previous article, after subcutaneous inoculation of *T. cruzi*, the parasites penetrate the cells of the region and multiply there. Those invaded are the cells of the "peripheral reticulum" and the clasmatocytes. In the dog the region of inoculation is intensely parasitized by the 5th day. Amongst the cells particularly invaded are those constituting the sheaths of the striated muscles and sometimes even the muscular fibres themselves. The clasmatocytes are the cells most frequently parasitized. On the 12th day the lymphatic glands have been found to be heavily invaded. As the disease progresses, the trypanosomes spread to all the organs. Generally speaking, it can be said that the cells parasitized belong in great part to the

histiocytic-reticulum, comprising the reticular cells of the haemo-lympho-poietic organs and of the endothelium, and the clasmatocytes.

T. cruzi is, however, not entirely a parasite of the reticulo-endothelial system, but is adapted to other cells, particularly muscle fibres, testicular cells, etc. This is in contrast with Leishmania which is more exclusively adapted to the reticulo-endothelial system. The author considers that the adaptation of *T. cruzi* for the other cells mentioned is only rendered possible as a result of its adaptation to the reticulo-endothelium. *W. Y*

VILLELA (Eurico) & VILLELA (Eudoro). [In Portuguese & English.] Elementos do sistema nervoso central parasitados pelo *Trypanosoma cruzi.* **Elements of the Central Nervous System parasitized by** *Trypanosoma cruzi.*—*Mem. Inst. Oswaldo Cruz.* 1932. Vol. 26. No. 1. In Portuguese pp. 77–79. In English pp. 80–81. With 11 figs. on 2 plates.

VIANNA was the first to show that the neuroglia cells are infected by *T. cruzi*, but recent work has shown that it is not the only cell to be involved. Up to the present the nerve cells themselves were believed not to be parasitized, but the work of the authors has convinced them that these cells may be infected by *T. cruzi*, and figures are given showing pyramidal cells from a dog's cortex full of parasites. The authors believe that the particular strain used by them, viz. the *Tatusia* strain, exhibits a distinct neurotropism ; and they actually found that in dogs infected with this strain the parasites abound in the central nervous system and are rare in the heart muscle. *W. Y.*

MAZZA (Salvador). *Triatoma geniculata* agent de transport de *T. cruzi*. Nouveaux cas de fièvre de Malte en Argentine. [*T. geniculata*, **Carrier of** *T. cruzi* **in the Argentine.**]—*Bull. Soc. Path Exot.* 1932. Feb. 10. Vol. 25. No. 2. pp. 145–146.

The author records the discovery of *Triatoma geniculata* at Florencia situated in the north of Santa Fé. This Triatoma lives in the burrows of *Dasypus novencinctus* which explains the frequency of natural infections of *T. cruzi* in them. *W. Y.*

MURAZ (G.). Quelques derniers mots au sujet de la "Cure-standard" de la maladie du sommeil. [**Last Words on the Standard Cure of S.S.**]—*Bull. Soc. Path. Exot.* 1932. Jan. 13. Vol. 25. No. 1. pp. 39–43.

In this article the author continues, and presumably winds up, the polemic on this subject. [For previous references see this *Bulletin*, Vol. 27, p. 814, Vol. 28, pp. 351 and 352, and Vol. 29, p. 287–8]. *W. Y.*

HECKENROTH. Le traitement de la trypanosomiase humaine africaine, à *T. gambiense*. [**Treatment of** *T. gambiense* **Infection.**]—*Arch. de Méd. Gén. et Colon.* formerly *Rev. Méd. de France et des Colonies.* 1932. Feb. Vol. 1. No. 2. pp. 79–84.

This is an article of a general nature dealing with the various drugs of use in the treatment of human trypanosomiasis. It requires no special notice. *W. Y.*

BROWNING (C. H.), COHEN (J. B.), ASHLEY (J. N.) & GULBRANSEN (R.). **The Antiseptic and Trypanocidal Action of Certain Styryl and Anil Quinoline Carboxylamides.**—*Proc. Roy. Soc.* Ser. B. 1932. Apr. 1. Vol. 110. No. B767. pp. 249–260.

This is a chemical paper of a technical nature and should be consulted in the original by those interested. *W. Y.*

DELBREIL (Jean). Sur un cas de maladie du sommeil avec formol-leucogel-réaction positive, négativée par la tryparsamide. [**Case of S.S. with Formol Gel Reaction negatived by Tryparsamide.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1932. May 30. 48th Year. 3rd Ser. No. 18. pp. 760–763.

Details are given of a case of sleeping sickness, successfully treated with tryparsamide, in which a strongly positive formol-gel reaction disappeared during the course of treatment. *W. Y.*

COHEN (Aaron), KING (Harold) & STRANGEWAYS (Winifred I.). Trypanocidal Action and Chemical Constitution. Part X. Arylthioarsinites.—Reprinted from *Jl. Chem. Soc.* 1931. pp. 3043–3057.

COHEN (Aaron), KING (Harold) & STRANGEWAYS (Winifred I.). Trypanocidal Action and Chemical Constitution. Part XI. Aromatic Arsonic Acids containing Amide Groups.—Reprinted from *Jl. Chem. Soc.* 1931. pp. 3236–3257.

COHEN (Aaron). Trypanocidal Action and Chemical Constitution. Part XII. Arylthioarsinites derived from κ-Thiolundecoic Acid.—Reprinted from *Jl. Chem. Soc.* 1932. pp. 593–598.

SAUNDERS (G.) & MORRIS (K. S.). Suggestions for the Control of Human Trypanosomiasis.—*West African Med. Jl.* 1932. Apr. Vol. 5. No. 4. pp. 62–64.

TUBANGUI (Marcos A.) & YUTUC (Lope M.). The Resistance and the Blood Sugar of Animals infected with *Trypanosoma evansi.*—*Philippine Jl. Sci.* 1931. May. Vol. 45. No. 1. pp. 93–107. With 7 text figs. [15 refs.]

BLACKWATER FEVER.

OTT. Recherches sur la pathogénie et le traitement de la fièvre bilieuse hémoglobinurique. [**Researches on the Pathogeny and Treatment of Blackwater.**]—*Bull. Soc. Path. Exot.* 1932. May 11. Vol. 25. No. 5. 494–512.

The author has asked himself whether decrease in the red cell resistance in certain cases of chronic malaria may not pave the way for the haemoglobinuric crisis by rendering the red cells sensitive to the action of numerous toxic substances, endogenous or exogenous, biological or chemical, arising spontaneously or introduced in some manner (alimentary, therapeutic). He has also inquired what part the cholesterinaemia factor plays in the variations of this resistance and whether cholesterol is of any therapeutic value. He points out that haemolysis is an abnormal phenomenon, to some extent controlled by the experimenter in whose hands the red cell is caused to yield up its haemoglobin under the influence of the most diverse reagents. He considers therefore it is desirable to ascertain what happens to the red cell when tested against a great number of haemolytic agents and not to limit oneself, as has become a custom, to the measurement of its resistance to hypotonic saline. Then again there are various known substances which exert a protective action on red cells; amongst these cholesterin has a biological importance.

In the first part of his work the author has determined the red cell resistance (cholesteraemia being in action) of Annamites—healthy, malarial and haemoglobinuric—against the following three kinds of haemolytic reagents:—(*a*) Physical agent: hypotonic saline. (*b*) Chemical agent: three salts of quinine. (*c*) Biological agent: anti-human sera.

Full details are given of the technique employed and the results of the observations are set forth in tabular form.

The next section of the paper relates to the subject of cholesteraemia and the manner in which hypercholesteraemia can be provoked. Finally, the author passes to a consideration of the effects of induced hypercholesteraemia on the red cell resistance. [For details this interesting paper must be consulted in the original.]

The author summarizes his conclusions as follows:—

1. *Red cell resistance.*

A. In the normal Annamite the red cell resistance is equal to that of the normal European.

B. In the Annamite infected with malaria: (*a*) The resistance to hypotonic saline varies in different individuals; it is often diminished, especially in the pyrexial period, but sometimes also during the height of the fever. (*b*) The resistance to the quinine salts does not exhibit any modification from the normal.

C. During blackwater fever red cell fragility is the rule. (*a*) Against hypotonic saline this is very marked; (*b*) Against the quinine salts the resistance is normal, with the exception of quinine formas towards which there is in the course of blackwater fever an elective fragility of the red cells.

II. *Cholesteraemia.* This must be estimated not only in the serum, but also in the red cells.

A. In the normal Annamite the degree of cholesteraemia is definitely less than in the normal European; this is undoubtedly a matter of race, but it is also one of alimentation.

B. In malaria a hypocholesteraemia, more or less pronounced, appears to be the rule.

C. In blackwater fever this hypocholesteraemia is still more pronounced.

III. *Induced hypercholesteraemia.* This is easy to produce by injection of cholesterin in oily solution; it ought to be measured not only in the serum but also in the red cells. It arises from a superactivity of the cholesteringenetic centres which are stimulated by the infection. It is often not apparent in the serum, but it manifests itself by a surcharge of the red cells with cholesterin; this is especially marked in the haemoglobinuric.

IV. *Effects of induced hypercholesteraemia on the red cell resistance.*

A. The hypercholesteraemia is followed after some hours by an increase in the red cell resistance to hypotonic saline; this is seen equally well in the haemoglobinuric as in the malarial subject.

B. Increase of resistance to the quinine salts is only seen in the haemoglobinuric and only in respect of the quinine formas.

C. Contrary to the effect which it has on the other haemolytic agents, hypercholesteraemia sometimes results in a diminution of the red cell resistance to the haemolysins of antihuman sera.

W. Yorke.

BRAHMACHARI (Upendranath), BRAHMACHARI (Phanindranath) & BANERJEA (Radhakrishna). **Studies in Black-Water Fever.**—*Amer. Jl. Trop. Med.* 1932. Mar. Vol. 12. No. 2. pp. 117–122.

Whatever may be the mechanism of blackwater fever, there is no doubt that there are many cases in which quinine is a determining factor and its administration may be followed by severe haemoglobinuria, while in other cases quinine has little or no influence upon the disease. The authors state that the disease may therefore be classified as follows:—

"1. *Quinine-intolerant type.* This includes cases in which haemoglobinuria is precipitated by the administration of quinine. It can be subdivided into two groups:

"(*a*) *Mild* in which the haemoglobinuria stops as soon as quinine is discontinued.

"(*b*) *Severe* in which haemoglobinuria persists after the discontinuance of quinine and the condition may end fatally.

"2. *Quinine-tolerant type.* This includes cases in which haemoglobinuria has little or no relationship with administration of quinine."

Details are given of a case of malaria in which it was possible experimentally to evoke haemoglobinuria, the degree of which could be varied by increasing or diminishing the dosage of quinine. The patient, a boy of six years of age, was intolerant to almost any dose. When he came under observation, he was suffering from malignant tertian malaria, the spleen was enlarged, and the blood contained *P. falciparum.* The following observations were made:—

(1) Quinine bihydrochloride, $\frac{1}{12}$ grain, twice a day gave rise to frequent yawning, weakness, and faint haemoglobinuria.

(2) Quinine bihydrochloride, 1 grain, gave rise to pain in the abdomen and limbs, well-marked haemoglobinuria, jaundice, and a distinct rise of temperature.

(3) Quinine bihydrochloride, 2½ grains, was followed by a quick and feeble pulse, intense pain in the limbs and abdomen, great prostration, marked haemoglobinuria and jaundice, and a temperature up to 105°F. These somewhat alarming symptoms subsided in 48 hours.

(4) Quinine bihydrochloride, 5 grains, was followed by intense haemoglobinuria, very severe prostration, and drowsiness. The condition was almost fatal.

The authors point out that the treatment of malaria in cases of this type is evidently one of the most difficult problems in tropical medicine.

The second part of the paper consists of observations on the action of quinine on erythrocytes in cases of blackwater fever. The author adopted the usual technique of mixing a suspension of washed erythrocytes in saline with ascending strengths of quinine hydrochloride. The following are in substance the conclusions :—

The erythrocytes in blackwater fever are slightly more vulnerable to quinine than those of normal individuals, and equally so before, during, and after disappearance of the haemoglobinuria. The increased vulnerability is so slight that it cannot account for blackwater fever following quinine administration. *W. Y.*

MANOUSSAKIS (E.). Hémoglobinurie quinique et bilieuse hémoglobinurique. [**Quinine Haemoglobinuria and Blackwater Fever.**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1931. July 20. Year 47. 3rd Ser. No. 25. pp. 1422–1426.

After mentioning general reasons why, in his opinion, quinine haemoglobinuria should be distinguished from blackwater fever, the author states that he has had the opportunity of studying a considerable number of cases of each disease, and that he proposes to indicate briefly the points whereby the two—which have nothing in common except the colour of the urine—can be distinguished.

Details are given of the case of a soldier, who contracted malaria in 1917, and continued to suffer from it until 1921, because each attempt at quinine treatment was followed by an attack of haemoglobinuria. He was only cured when he left his native country and went to live in Piræus. When he was subsequently mobilized he reported his quinine idiosyncrasy. It was decided to test his reaction to quinine and on 28th Dec. (1930 ?) an injection of 0·1 gm. was given ; this dose was well tolerated, but a further injection of 0·25 gm. of quinine provoked a serious attack of haemoglobinuria. Twenty-two hours later, when the urine had cleared, but still gave the Mayer reaction for quinine, a further injection of 0·25 gm. of quinine was injected without ill effect. For the next three days 0·35 gm. of quinine was given daily and was not followed by haemoglobinuria. The quinine was then stopped until 8th Jan., when 0·25 gm. was injected ; this was followed by haemoglobinuria. The same evening, before the urine had quite cleared, another dose of quinine was given ; and as this was not followed by haemoglobinuria, the administration of quinine was continued.

From this case and others of a similar nature, it appears that :—

1. None of these persons have made use of quinine previous to that provoking the first attack of haemoglobinuria ; and this has appeared in all of them after the first dose of the medicament.

2. All cases have had several attacks of haemoglobinuria, and this accident has supervened each time they have attempted to return to quinine.

3. The haemoglobinuric crisis has always occurred within 1½ hours of each dose of quinine, and the intensity of the attack was proportional to the amount of the drug. The haemoglobinuric crises in these cases exhibit the fundamental characters that they invariably occur each time quinine is given after the total elimination of the previous dose, and that they do not occur when quinine is given before the elimination of the previous dose. [See also page 312.]

In the author's view these characters suffice to distinguish quinine haemoglobinuria from blackwater. There are, however, others. In the former condition there is leucopenia with monocytosis. Haemoglobinaemia is constant in blackwater, but never seen in quinine haemoglobinuria. The red cell resistance is always very feeble during the crisis and often after the crisis in quinine haemoglobinuria, whilst in true blackwater the author has never seen lowered resistance.

Clinically the two conditions are quite different. The blackwater patient becomes a veritable human wreck within a few hours, whilst the quinine haemoglobinuric patients remain in good condition. Finally, true blackwater is a condition which occurs only in malaria patients and most frequently in those of long standing, irregularly and imperfectly treated, and spares those regularly treated; it occurs in those who have already taken quinine for many years without ill result, and relapses are exceptional. Quinine haemoglobinuria, on the contrary, depends on a single and unique factor, viz., the absorption of quinine at a time when it is not already present in the circulation. It occurs in a patient infected with malaria or in one who is not infected, and lastly it appears after the first sufficient dose of the drug, and relapses occur every time the drug is given in an intermittent manner.

W. Y.

SAMPSON (B. F.). **Blackwater Fever and its Relation to Malaria.**—*South African Med. Jl.* 1932. May 28. Vol. 6. No. 10. pp. 323–329. [26 refs.]

In this paper, which is speculative, the author elaborates a hypothesis to explain the development of blackwater fever. He states that his object is chiefly to direct a closer scrutiny to a corner of the subject that does not appear to have received sufficient attention, viz., what happens to an individual during those essential previous months in a blackwater area before the advent of his first attack? The author accepts the view that malignant tertian malaria is a *sine qua non* in the development of blackwater, but the incidence of this disease does not always correspond with the intensity of endemic subtertian malaria. The death rate from malaria may be high, and blackwater fever conspicuous by its absence. In contradistinction there exist so-called "blackwater areas" where, for some reason or other, cases are plentiful. Obviously, there must be some factor to explain this. Another baffling problem is that the occurrence of blackwater appears in some curious way to be connected with the arrival of the white settler in certain endemic districts, previous to which the indigenous natives, though heavily infected with subtertian malaria, were singularly free from blackwater. These natives had previously acquired a malarial immunity, so that the advent subsequently of blackwater amongst them is all the more curious. The author asks what connexion can there be between blackwater and the association of the European: and why it is that an immune native, in the ordinary way, does not get blackwater, though

he probably picks up many abortive *P. falciparum* infections? If one takes the attitude that before he can get blackwater he must lose his malarial immunity, then one immediately comes up against the question of how association with a white man affects this question of immunity in natives. The author discusses at considerable length the question of the development of immunity in untreated malaria, and considers that there is some evidence that the reticulo-endothelium is the antibody producer. He remarks that the repeated painting of the skin of a mouse with tar will ultimately produce epithelioma, and he contends that in blackwater fever we have the same thing happening in a chemical sense. Being stimulated or irritated to exhaustion, the reticulo-endothelium liberates a precursor of antibody, which is the haemolytic substance described by NOCHT. In its exhausted state this is the only response it can make; it will occur sometimes after quinine without fever, and sometimes in fever without quinine.

The author sums up his views in the following way :—

"With what, therefore, are we left? At least a fair basis for suspicion that quinine has some very serious effect on the immunity mechanism. It is my belief that its action is one of irritation upon specialized tissue, the function of which, in the ordinary way, being the production of these antibodies [*sic*]. But the product of irritation is not the normal antibody, and yet it has with antibody the common property of being destructive to trophozoites. Moreover, the evil effect of such irritation is particularly marked if it is allowed to operate on this delicate tissue before the specific antibody function has had time to establish itself. And this brings me down to the vital point in the production of blackwater. Given a sufficient intensity of endemic subtertian fever, the first milestone to haemoglobinuria is laid with the thorough and immediate treatment by quinine of the first attack of this type of fever. It may be that the treatment successfully destroys the whole infection. The next parasite picked up by the unfortunate individual may very well be a *Plasmodium vivax*, but this is not essential. It will require considerable quinine, and by the time two or more relapses have been dealt with, his general health will be considerably depressed. Should he now commence substituting vital food elements with alcohol, the level of his general resistance will depreciate still further, but this also is not essential. Put in now another infection with *Plasmodium falciparum*. This is likely to hit him hard, both in consequence of the depressed state of his antibody mechanism and by reason of the low tone of his non-specific resistances. The withholding of quinine at this juncture would be asking for trouble, but the giving of it in adequate doses would be the passing of another milestone to blackwater. It is difficult to assess just how much quinine and subtertian malaria is required in any one individual to bring his immunity mechanism to that state of irritation and depression which is the immediate pre-blackwater state. But there comes a time when the next demand on this specialized tissue will be answered by the production of precursor or immature antibody, and this may be the answer made to any one of the following :— (1) Quinine without fever. (2) Fever without quinine. (3) Quinine and fever. (4) Exposure to cold, trauma, fatigue, other illnesses, etc." *W. Y.*

LECLEF. Onze cas de bilieuse hémoglobinurique chez les noirs. [**Eleven Cases of Blackwater in Negroes.**]—*Ann. Soc. Belge de Méd. Trop.* 1931. Aug. 31. Vol. 11. No. 3. pp. 293–310. With 11 charts. [1 ref.]

Within a period of six months the author has had under observation in hospital at Kipushi, 11 cases of blackwater fever in natives. The

patients were all Banyaruandas or Barundis and had been recruited in the territory of Ruanda-Urundi. These natives are heavily infected with malaria. Prophylactic quinine (0·5 gm.) is given daily to the labourers, and as they appreciate the benefit there is no difficulty in getting them to take it. In spite of this quininization, however, the entries to hospital for malaria are numerous.

Of the 11 cases of blackwater, 9 occurred among the surface workers, who were unfit for work underground and who did not take prophylactic quinine. The attack in every instance followed the administration, for an attack of malaria, of a large dose (1 to 2 gm.) of quinine. Clinical details and temperature charts of the various cases are given.

W. Y.

DE DECKER. Quelques observations de fièvre bilieuse hémoglobinurique chez le noir. [**Blackwater Fever in the Negro.**]—*Ann. Soc. Belge de Méd. Trop.* 1932. June 30. Vol. 12. No. 2. pp. 213–224. With 8 charts.

Reference is made to the fact that in 1931 LECLEF notified nine cases of blackwater fever in natives at Kipushi, Katanga. Since the end of March, 1931, the author has had charge of 17 additional cases. In all except one malaria parasites were found in the blood. LECLEF had concluded that the attack of blackwater in his cases was provoked by the administration of large (1 to 2 gm.) doses of quinine, but Decker does not entirely share this view. He considers that the main cause is an individual predisposition in a greatly debilitated malarial subject. All his patients were either debilitated females or surface labourers who had been several times in hospital for malaria or other diseases.

Amongst his small group of cases Decker encountered three relapses and probably he might have seen more had he not made a point of repatriating the convalescents. It is remarked that the exciting dose of quinine was, as a rule, the same as, or even less than, the dose which the patients had previously taken as a prophylactic against malaria. In contrast to LECLEF the author was in the habit of giving his malaria cases relatively small doses of quinine, viz., 0·5 gm. on the first day of admission to hospital, 1·0 gm. on the second day and 1·5 gm. on the third day. Of nine cases, in whom the disease developed after admission to hospital, it occurred before any quinine had been taken in four and in two others after only 0·5 gm. From May onwards all the author's patients had taken regularly 0·75 gm. of quinine twice weekly as a prophylactic. In view of the great number of people admitted to hospital for malaria in Ruanda, it was decided in April to administer prophylactic quinine,and on Tuesdays and Fridays all—men and women alike—were given 0·75 gm. of quinine under the direction of a white supervisor. The author writes that on the one hand he gave 0·75 gm. of prophylactic quinine to 900 men and 500 women, practically all of whom had malaria, without the production of any blackwater fever, and on the other hand some attacks occurred without any quinine and others after only 0·5 gm. in people who had previously taken their prophylactic quinine with impunity.

With regard to treatment, the author states that, immediately a diagnosis was made, quinine was stopped and replaced by plasmochin; when the urine had cleared this was in turn replaced by plasmochin-quinine compound. As a routine 10 to 20 cc. of antivenom serum was given; the author adds that he is not strongly convinced of the efficacy

of this and that two of his cases got better without it. Of the 17 patients three died. The temperature charts and other details are given in respect of nine of the cases. *W. Y.*

MICKANIEWSKI. Contribution à l'étude de la fièvre bilieuse hémoglobinurique (à propos de cinquante cas observés sur les hauts plateaux annamitiques). [**Blackwater Fever in Annam.**]—*Bull. Soc. Méd.-Chirurg. Indochine.* 1931. Sept. Vol. 9. No. 8. pp. 664–690. [3 pages of refs.]

During a sojourn of nearly five years in the high plateaux of Kontum and Darlac, the author has had under observation 50 cases of blackwater fever. This paper consists of a lengthy and general account of the disease ; it contains no new facts and requires no special notice in this *Bulletin*. [It is interesting to note that although a long list of references is given every one of them is French.] *W. Y.*

TSCHERGECHTOW (A. S.). [**Blackwater Fever in Gandja (Caucasus).**]—*Trop. Med & Vet.* Moscow. 1930. Vol. 8. No. 10. pp. 7–12. [In Russian.]

The author describes seven cases of blackwater fever observed in Gandja ; this condition is very rare in the Caucasus, and the present cases were the only ones seen by the author during the last four years in the course of which 11,000 cases of malaria were examined. The conclusions are as follows : All the cases observed are closely associated with malaria ; any form of malaria can bring about this condition, but it is especially frequent in cases of malignant tertian ; blackwater fever is frequently associated with haemorrhagic phenomena ; in two cases the symptoms of haemoglobinuria developed independently of quinine, and in one it could be attributed to quinine idiosyncrasy.

C. A. Hoare.

DE RAYMOND (A.). Note thérapeutique sur le traitement de la bilieuse hémoglobinurique par le chlorhydrate de choline. [**Treatment of Blackwater Fever by Choline Hydrochloride.**]—*Bull. Soc. Path. Exot.* 1932. Mar. 9. Vol. 25. No. 3. pp. 215–221.

The author considers that it would be extremely interesting to know the degree of cholesteraemia in blackwater fever patients and to ascertain if there is any relationship between the haemolysis and a definite decrease of blood cholesterin. The author himself has only been able to make observations at Hanoï on chronic malaria cases evacuated from the upper regions ; and the amount found by PIERIER, using the method of Grigault, varied from 0·35 cgm. to 0·9 cgm. per litre. PONS, ADVIER, BOREL and GUILLERM have obtained similar results and are of the opinion that hypocholesteraemia is the rule in malaria [see this *Bulletin*, Vol. 23, p. 553]. Unfortunately, the amount of cholesterin present in the blood of patients actually suffering from blackwater fever has yet to be ascertained.

There is, in the author's mind, no doubt that injections of cholesterin are of real value in blackwater fever. These injections, however, suffer from the great disadvantage that they are made with an oil solvent and are consequently but slowly diffusible and of delayed action. In blackwater it is necessary to act quickly ; the access is sudden and the course is often short.

It occurred to the author that the proper procedure is to encourage if possible cholesterogenesis. The researches of CARLOS and LEURET on the action of chlorhydrate of choline on the production of blood cholesterol have incited De Raymond to use this product in blackwater fever. He claims that success has awarded his efforts. Cholesterogenesis is stimulated, the degree of cholesteraemia rises and haemolysis is immediately impeded. The diffusion of the medicament is extremely rapid, as is shown by the clinical records appended. DE PALMAS claims that in four cases the haemoglobinaemia ceased within an hour of the injection.

Treatment consists in one or two subcutaneous injections of 2 cgm. of chlorhydrate of choline (Biocholine) daily until disappearance of the cardinal signs and arrest of haemoglobinuria.

Details, supplied by various of the author's colleagues, are given regarding nine cases of blackwater fever treated with the drug. [Whether, however, the author's claim " il semble bien que le chlorhydrate de choline agisse d'une façon certaine sur la disparition de l'hémoglobinurie " is justifiable remains to be seen.] *W. Y.*

LAZZARO (Giuseppe). Sulla cura della malaria nell'emoglobinuria da chinina. [**The Treatment by Quinine of Malaria in Haemoglobinuric Patients.**]—*Riv. di Malariologia.* 1931. May-June. Vol. 10. No. 3. pp. 269–280. [16 refs.] English summary (8 lines) pp. 419–420.

To give or withhold quinine in the treatment of blackwater fever or in those suffering from malaria who have had blackwater is a subject of ever-recurring interest. The author quotes the varying opinions of the last half century and records six cases of his own. In four of these *P. falciparum* was present, in one *P. vivax*, and in the other parasites could not be found. The author's procedure is to give quinine [salt not stated] " in therapeutic doses," 1–2 gm. in the cases detailed, and to continue it to prevent relapse and cure the malaria. He maintains that quinine given during the attack of haemoglobinuria and for a day or two after does not aggravate the attack nor tend to cause relapse.

H. H. S.

TAYLOR (C. J. S. O.) & RUSSELL (H.). **Blackwater Fever and Naphthalene Poisoning.**—*West African Med. Jl.* 1932. Jan. Vol. 5. No. 3. pp. 48–49.

Details are given of a case of naphthalene poisoning, the result of swallowing two ground-up camphor balls. The case is recorded because it was at first diagnosed as probably blackwater fever. *W. Y.*

SCHACHSUWARLY (M.). Beitrag zur Frage der paroxysmalen Hämoglobinurie. [**Paroxysmal Haemoglobinuria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1932. June. Vol. 36. No. 6. pp. 336–343. [24 refs.]

Clinical details are given from Baku of two cases of paroxysmal haemoglobinuria which came under the author's observation during the early part of 1930.

Case 1. A man aged 30 ; family history good, no history of syphilis or tuberculosis. Felt ill first in 1924 ; since then has had many rigors, accompanied by fever and dark urine. The attacks were chiefly in the winter after exposure to cold. Since 1924 he has suffered from malaria ; quinine

was well tolerated, but the doctors in Baku and Tiflis warned him against it. A detailed account is given of the condition of the patient on admission to hospital. The Wassermann, Sachsgeorgi and Kann reactions were strongly positive, and the blood contained *Plasmodium falciparum* and *Plasmodium malariae.*

Case 2. A man aged 40; family history good, syphilis in 1921. In 1925, after exposure to heavy rain, he had a rigor accompanied by fever and dark urine. Since then he has had each winter 5 or 6 severe attacks of paroxysmal haemoglobinuria. An account is given of the condition on admission to hospital. The Wassermann, Sachsgeorgi and Kann reactions were strongly positive, but there was no evidence of malaria.

Both patients gave the Ehrlich and the Donath and Landsteiner reactions.

The first problem to be faced in Case 1 was to cure malaria. With this object in view a small dose of quinine was given and, as this had no untoward action, the usual dose of 1 gm. was given the next day, and in addition plasmochin. Then, for several days 2 gm. of quinine was given. Similarly quinine was well tolerated by Case 2. Hence the author was able to confirm the observations of MANNABERG and DONATH that quinine does not provoke haemoglobinuria in this disease.

A paroxysm was produced by means of a foot-bath and a number of observations made throughout the course of the attack. These, which relate to the changes in temperature, the blood pressure, the blood catalysis, the leucocyte formula and the urine findings, are given in a couple of tables.

The following summary is given :—

The etiology of paroxysmal haemoglobinuria is syphilis and an abnormal innervation of the vessels, but not malaria. The malaria attacks did not provoke a paroxysm of haemoglobinuria, nor did the administration of quinine. The autolysin titre was not influenced by quinine in either patient. The exciting causes of an attack of paroxysmal haemoglobinuria are cold, hot water, adrenalin, and excitement. In an attack of paroxysmal haemoglobinuria, the characteristic features are rigor, fever, albuminuria, haemoglobinuria, increase of blood pressure and leucocyte changes. Expecially important is a general leucocytosis, accompanied by a lymphopenia and a decrease of monocytes and eosinophils. These leucocyte changes are seen even in abortive attacks. The severity of the disease is dependent on the haemolysin titre. Papaverin treatment modifies certain of the symptoms, but does not influence the haemolytic process. *W. Y.*

GHIRON (Mario). **On Blackwater Fever.**—*Jl. Trop. Med. & Hyg.* 1932. Mar. 1. Vol. 35. No. 5. pp. 65–71.

This is a translation of a paper published in German in 1927, which was noticed in this *Bulletin*, Vol. 24, p. 657. The translation is described without qualification as an " Original Communication." *A. G. B.*

GHOSAL (J. N.). Four Types of Blackwater Fever seen in the Mofussil of Bengal. —*Calcutta Med. Jl.* 1932. Feb. Vol. 26. No. 8. pp. 322–327. With 1 chart.

LOUVEAUX (L.). Observation d'un cas d'hemoglobinurie chez un noir.—*Bull. Méd. du Katanga.* 1930. Vol. 7. No. 5. pp. 129–130.

REYNOLDS (Fredrick H.). A Case of Blackwater Fever precipitated by Ptomaine Poisoning due to Unclean *Degchies.—Indian Med. Gaz.* 1932. Apr. Vol. 67. No. 4. pp. 198–199.

SUÁREZ (Ramón M.). Fiebre hemoglobinurica en Puerto Rico.—*Bol. Asoc. Med. de Puerto Rico.* 1931. Oct. Vol. 23. No. 193. pp. 363–379. [23 refs.]

WEIL. Observations on Blackwater Fever in Galilee.—*Harefuah.* Jerusalem. 1930. Sept.-Oct. Vol. 4. No. 5. p. 259.

REVIEWS AND NOTICES.

BUROWA (L. F.) & KASSIRSKY (I. A.). **Tropical Diseases in Middle Asia.**—242 pp. With 49 figs. 1931. Moscow–Tashkent: State Publication. [In Russian.]

This is an elementary text-book of tropical diseases, specially adapted to the requirements of medical officers practising in Russian Middle Asia. The diseases dealt with are mainly those caused by animal parasites (malaria, leishmaniasis, amoebiasis, lambliasis, balantidiasis, coccidiosis, relapsing fever, fasciolasis, ankylostomiasis, strongyloidosis, guinea-worm infection). The only other diseases described are sprue, pellagra, and papataci and undulant fevers. An account is given of the aetiology, clinical aspects, pathological anatomy, epidemiology and treatment of each disease. The book is in every respect below the standard of similar text-books published in Europe and America. The authors appear to have no clear notion of the systematics and nomenclature of the parasites described. Thus, the dysentery amoeba is referred to in one place as *Entamoeba dysenteriae*, and in others as *Amoeba histolytica*, while *Iodamoeba bütschlii* is made to represent the genus *Pseudolimax*. The book abounds in misprints, the paper on which it is printed is deplorable, while th illustrations are so defective that little would be lost if the majority had been left out altogether. The majority of references to literature are of Russian works.

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